National Institute for Health and Clinical Excellence

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Tuberculosis

Clinical diagnosis and management of tuberculosis, and measures for its prevention and control

This is the full version of NICE clinical guideline 117. It contains details of the methods and evidence used to develop the guideline. It updates and replaces the full version of 'Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control' that was developed by the National Collaborating Centre for Chronic Conditions and published by the Royal College of Physicians in March 2006. The updated recommendations have been developed by the Centre for Clinical Practice at NICE following the NICE short clinical guideline process.

NICE clinical guideline 117

Developed by the National Collaborating Centre for Chronic Conditions and the Centre for Clinical Practice at NICE

This guidance updates and replaces 'Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control' (developed by the National Collaborating Centre for Chronic Conditions [now the National Clinical Guideline Centre] and published by the Royal College of Physicians in March 2006).

New recommendations on the use of interferon-gamma tests for the diagnosis of latent tuberculosis have been added. Updated recommendations have been developed by the Centre for Clinical Practice at NICE.

A grey bar in the righthand margin indicates text from the 2006 guideline and text that was added or updated in 2011.

- **2006** indicates that the evidence has not been updated and reviewed since the original guideline.
- **2006, amended 2011** indicates that the evidence has not been updated and reviewed since 2006 but a small amendment has been made to the recommendation.
- **new 2011** indicates that the evidence has been reviewed and the recommendation has been updated or added.

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Contents

2006, amended 2011

Background

New 2011

In 2006 the National Collaborating Centre for Chronic Conditions published guidance on the clinical diagnosis and management of tuberculosis (TB), and measures for its prevention and control. In this guidance the section on the diagnosis of latent TB has been updated by the Short Clinical Guidelines team within NICE. Grey bars in the right hand margin indicate whether the section has been updated (2011) or is from the original guideline (2006).

Preface - 2006

2006

Tuberculosis, or TB, is one of man's oldest foes and for centuries among the most feared. One of the triumphs of modern medicine has been the development of vaccination and medication capable of combating this ancient disease, and it now rarely troubles the thoughts of those born into modern Western society. Yet TB remains capable of exciting occasional major concern, for example when reports of local outbreaks emerge, and this continuing wariness is appropriate. Although TB notifications fell steadily for most of the twentieth century, this fall was not maintained in the last decade. Some racial groups have much higher TB incidence than others and, irrespective of ethnicity, the disease is more common in those in deprived social circumstances. Moreover, there are huge reservoirs of TB elsewhere in the world, with the additional spectre of growing pockets of infection resistant to available treatment. For all these reasons it is still necessary to focus attention on the optimum management of TB, and that is the purpose of this guideline.

The guideline has been commissioned by NICE as a successor to the British Thoracic Society's TB guidelines, which have been used with great benefit for many years as the principal source of advice on TB management in the UK. The scope of the guideline is unusually wide, and we were obliged to divide the work between two separate guideline development groups, one covering diagnosis and management, the other prevention and control. Both groups used what has become our standard methodology, first identifying the key aspects of the disease and then searching out and appraising the best

relevant evidence. In some areas, particularly those around prevention and control, it has been unusually difficult to find strong evidence. In all cases the guideline groups have attempted to produce practical recommendations, however much or little evidence they had to work on. In addition, great efforts were made to link the advice contained in the guideline to that available from other sources, in particular advice from the Joint Committee on Vaccination and Immunisation.

Although TB will not affect the majority of the UK population, some of the recommendations in the guideline will do so. For years, all secondary school children have been given Bacille Calmette-Guèrin (BCG) vaccination through the schools programme. The current epidemiology of TB in the UK suggests that this is inappropriate and that vaccination efforts should be targeted towards those most at risk, with a change in emphasis towards offering BCG to neonates. This will bring challenges for implementation, and this is not the only recommendation in the guideline which will do so. Directly observed therapy is not necessary as a routine, but is appropriate in those unlikely to adhere to the required treatment regime. This will necessitate careful risk assessment. The guideline also recommends that all people with TB should have a key worker to help educate and promote treatment adherence. These measures are important to the individuals with TB and to the wider community since effective management of patients and contacts is critical to avoiding the development and spread of drug-resistant TB.

The two guideline development groups have each had to meet their own challenges in the development of this document. Their sincere desire to get the best for patients with TB has been evident to those of us involved in the administration of the project, and we are grateful to them for this commitment as well as their expertise. Particular thanks are due to the clinical advisor, Peter Ormerod, who sat on both groups. I believe their efforts have resulted in a comprehensive and authoritative guideline, which should serve the NHS well in the short and medium term and provide a firm basis for future development and improvement in TB management.

Dr Bernard Higgins MD FRCP

2006

Preface – 2011

New 2011

The 2006 guideline was reviewed for update in 2009, leading to a partial update that resulted in new recommendations for the diagnosis of latent TB (chapter 5).

In 2006 there was a lack of evidence available on the diagnostic utility of interferon-gamma tests (IGTs) and it was noted that there would need to be a partial update of the guideline to make recommendations on the use of IGTs for diagnosis of latent TB once additional evidence came available. The perception in 2006 was that this additional scientific evidence would have emerged by the time the guideline was due for review. There was also a concern that practice would have moved on and was then not in line with the recommended strategies. NICE concluded that because IGT is now commonly used the guideline should be updated but be only in the section(s) relevant to the use of IGT in the diagnosis of latent TB. Therefore, in October 2009 the Department of Health formally asked NICE to produce a short clinical guideline on interferon-gamma immunological testing for diagnosing latent TB (partial review of CG33).

1 Introduction

1.1 Background information

This guideline deals with activities undertaken by professionals in the NHS with the aims of diagnosing primary cases of tuberculosis (TB), identifying secondary cases, treating active disease, controlling latent infection and preventing further transmission. At a population level, the combined result of these activities should be to curb and then reverse the increase in TB seen in England and Wales in recent years. TB is a disease of poverty, and specific groups of the population are at heightened risk. To address this, the guideline provides recommendations, wherever there is evidence to support it, on ways

of organising services efficiently to provide the best possible care. Almost all cases of TB are preventable, and almost all people with TB can be cured.

What causes TB?

TB is caused by a bacterium called *Mycobacterium tuberculosis* (‘*M. tuberculosis*’ or ‘*M.Tb*’). It is spread by one person inhaling the bacterium in droplets coughed or sneezed out by someone with infectious tuberculosis. Not all forms of tuberculosis are infectious. Those with TB in organs other than the lungs are rarely infectious to others, and nor are people with just latent tuberculosis (see below). Some people with respiratory tuberculosis are infectious, particularly those with bacteria which can be seen on simple microscope examination of the sputum, who are termed ‘smear positive’. The risk of becoming infected depends principally on how long and how intense the exposure to the bacterium is. The risk is greatest in those with prolonged, close household exposure to a person with infectious TB.

What happens after infection?

Once inhaled the bacteria reach the lung and grow slowly over several weeks. The body’s immune system is stimulated, which can be shown by a Mantoux test[1], a common diagnostic technique. In over 80% of people the immune system kills the bacteria and they are removed from the body. In a small number of cases a defensive barrier is built round the infection but the TB bacteria are not killed and lie dormant. This is called latent tuberculosis; the person is not ill and is not infectious. Sometimes at the time of the initial infection, bacteria get into the blood stream and can be carried to other parts of the body, such as bones, lymph glands or the brain, before the defensive barrier is built. One third of the world’s population, two billion people, have latent tuberculosis.

If the immune system fails to build the defensive barrier, or the barrier fails later, latent tuberculosis can spread within the lung (pulmonary tuberculosis) or into the lymph glands within the chest (intrathoracic respiratory tuberculosis) or develop in the other part(s) of the body it has spread to

2006

[1] Tuberculin skin test (TST) has been replaced with Mantoux test, throughout the document

(extrapulmonary tuberculosis). Only some of those with latent tuberculosis will develop symptoms ('active tuberculosis'). About half the cases of active tuberculosis develop within a few years of the original infection, particularly in children and young adults. The other half of active TB cases arise from reactivation of the latent infection many years later.

Who catches TB?

Anyone can catch TB but those at particular risk are those who have been exposed to TB bacteria, and those who are less able to fight latent infection. They include:

- close contacts of infectious cases
- those who have lived in, travel to or receive visitors from places where TB is still very common
- those who live in ethnic minority communities originating from places where TB is very common
- those with immune systems weakened by HIV infection or other medical problems
- the very young and the elderly, as their immune systems are less robust
- those with chronic poor health and nutrition because of lifestyle problems such as homelessness, drug abuse or alcoholism
- those living in poor or crowded housing conditions, including those living in hostels.

What are the symptoms of TB?

Because TB can affect many sites in the body, there can be a wide range of symptoms, some of which are not specific and may delay diagnosis.

Typical symptoms of pulmonary TB include chronic cough, weight loss, intermittent fever, night sweats and coughing blood. TB in parts other than the lungs has symptoms which depend on the site, and may be accompanied by intermittent fever or weight loss. TB is a possible diagnosis to be considered in anyone with intermittent fever, weight loss and other unexplained symptoms. Latent tuberculosis without disease, however, has no symptoms.

How is TB diagnosed?

TB is diagnosed in a number of ways. Tissue samples from biopsies may show changes which suggest TB, as do certain X-ray changes, particularly on chest X-rays. Definite diagnosis is achieved by culturing the TB bacterium from sputum or other samples. This not only confirms the diagnosis, but also shows which of the TB drugs the bacterium is sensitive to. Mantoux test and IGTs can show if someone has been exposed to TB and may have latent infection. Skin tests use a tiny dose of TB protein injected under the skin. In people who have been exposed to TB this gives a positive reaction, which is seen as a raised, red area. IGTs involve taking a blood sample, which is processed at a laboratory.

How is TB treated?

TB is completely curable if the correct drugs are taken for the correct length of time. Before drug treatment for TB nearly half of all persons with active tuberculosis died from it. Several antibiotics need to be taken over a number of months to prevent resistance developing to the TB drugs. The great majority of TB bacteria are sensitive to the antibiotics used (rifampicin, isoniazid, pyrazinamide and ethambutol). A minority of cases, 6–8% in England and Wales, are resistant to one of the antibiotics. Isoniazid and rifampicin are ineffective in 1% of cases. These cases are said to be of multi-drug resistant TB (MDR TB), which is harder to treat (see Appendix G for details of TB epidemiology).

TB bacteria grow very slowly and divide only occasionally when the antibiotics start to kill them, so treatment usually has to be continued for six months to ensure all active and dormant bacteria are killed and the person with TB is cured. People with respiratory TB are usually not infectious after two weeks of treatment. Drug-resistant forms of the bacteria require treatment for longer than six months. MDR TB is particularly serious, requiring prolonged (up to 24 months) treatment, with the infectious period lasting much longer.

In latent tuberculosis there are many thousand times fewer TB bacteria than in active tuberculosis. Treatment with a single drug for six months, or two

2006

drugs for a shorter time, is sufficient to kill the dormant bacteria, preventing the person developing active tuberculosis later in their life.

Following TB treatment, the disease can return (relapse) in a small number of people, because not all bacteria have been killed. This is obviously much more likely if the course of treatment has been interrupted, not completed or otherwise not followed. However, it is also possible to catch TB a second time, unlike some other infectious diseases.

1.2 Epidemiology of TB in England and Wales

Detailed information on the epidemiology of tuberculosis is provided in Appendix G. Up-to-date epidemiological information, including reports of notifications and enhanced surveillance, is available from the Health Protection Agency (www.hpa.org.uk).

Historical trends

The TB notification system, implemented in 1913, showed that recorded TB rates peaked in England and Wales in the early part of the twentieth century, when 300 new cases per 100,000 people were reported every year. Since then, until the mid 1980s at least, the incidence of tuberculosis has been falling: in 1987 there were only 10 new cases per 100,000 people.

Geographical variations in incidence

There are marked differences in the incidence of tuberculosis in different parts of England and Wales, with most new cases occurring in cities. For example, there were 38 new cases per year per 100,000 population in London in 2001, as compared to less than five in the south west of England. There are also substantial variations in incidence of TB within cities, with as much as a thirtyfold difference between different London boroughs.

Variations in incidence by ethnicity and place of birth

Risk of TB is significantly higher in people from minority ethnic groups, as is evident in Table 1.

Table 1: Tuberculosis rates by ethnicity in England and Wales, 2001

Ethnicity	TB cases per 100,000 population
Black African	211
Pakistani	145
Indian	104
White	4

People born abroad were fifteen times more likely to contract tuberculosis as people born in England and Wales. The majority of cases in people born abroad occur after they have lived in the UK for several years.

2006

2 Methodology - 2006

2.1 Aim

With this document the National Collaborating Centre for Chronic Conditions (NCC-CC) has aimed to provide a user-friendly, clinical, evidence-based guideline for the NHS in England and Wales that:

- offers best practice advice for TB
- is based on best published evidence and expert consensus
- takes into account patient choice and informed decision-making
- defines the major components of the care provision for tuberculosis such as the diagnosis and management of both latent and active TB, and measures for its prevention and control
- indicates areas suitable for clinical audit
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for differing audiences (full version, short version, quick reference guide and public version) in electronic or printed format.

In contrast to most clinical guidelines commissioned by NICE, the prevention and control sections of this guideline include recommendations on service organisation where good quality evidence exists to support them.

2.2 Scope

The guideline was developed in accordance with a specified scope, which detailed the remit of the guideline originating from the Department of Health (DH) and specified those aspects of TB to be included and excluded.

Before development of the guideline began, the scope was subjected to stakeholder consultation in accordance with processes established by NICE.{1}(National Institute for Health and Clinical Excellence 2005) The scope is given in Appendix E.

2.3 Audience

The guideline is intended for use with the following people or organisations:

- all healthcare professionals
- people with, or at risk from, tuberculosis, and their carers
- patient support groups
- commissioning organisations
- service providers.

Involvement of people with TB

The NCC-CC was keen to ensure the views and preferences of people with TB and their carers informed all stages of the guideline. This was achieved by:

- consulting the Patient Information Unit (PIU) housed within NICE during the pre-development (scoping) and final validation stages of the guideline
- having two former TB patients and two user organisation representatives on the Guideline Development Group (GDG).

The patient and carer representatives were present at every meeting of the GDG. They were therefore involved at all stages of the guideline development process and were able to consult with their wider constituencies.

2.4 Guideline limitations

These include:

- the diagnosis and treatment chapters of this guideline (5–10), except rapid diagnostic techniques (5.3 and 5.4), do not cover issues of service delivery, organisation or provision (as this was not specified in the remit from the DH)
- NICE is primarily concerned with health services and so recommendations are not provided for Social Services and the voluntary

sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors

- generally the guideline does not cover rare, complex, complicated or unusual conditions.

2.5 Other work relevant to the guideline

Readers of this guideline should also be aware of the following publications:

- *Stopping tuberculosis in England and Wales*, the Chief Medical Officer's TB Action Plan{2}
- *Immunisation against infectious disease* (the 'Green Book'){3}
- *The clinical and cost-effectiveness of diagnostic tests for the detection of mycobacterial infection*, a health technology appraisal due for publication mid 2006 (see www.ncchta.org).

The National Knowledge Service is a relatively new national NHS body which is investigating ways of making patient and public information available to patients and the NHS, amongst other functions. One of the initial pilot projects is in tuberculosis, and is linked to this guideline. See www.hpa.org.uk/tbknowledge for more detail.

The Secretary of State for Health is advised on broader national policy on vaccination by the DH's Joint Committee on Vaccination and Immunisation (JCVI) (http://www.dh.gov.uk/ab/jcvi/index.htm).

Information on TB epidemiology in the UK and abroad, as well as some background information for patients and the public, is available through the Health Protection Agency's website at www.hpa.org.uk. This is referred to at relevant points in this guideline.

2.5.1 Related NICE guidance

Published

- Medicines adherence NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/cg76

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Tuberculosis: hard-to-reach groups. NICE public health guidance. Publication expected March 2012.

2.6 Background

The development of this evidence-based clinical guideline draws upon the methods described by the NICE Guideline Development Methods manual{1} (www.nice.org.uk/page.aspx?o=201982) and the methodology pack{4} specifically developed by the NCC-CC for each chronic condition guideline (http://www.ncgc.ac.uk/). The developers' roles and remit are summarised below.

National Collaborating Centre for Chronic Conditions[2]

The National Collaborating Centre for Chronic Conditions (NCC-CC) was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from the NICE.

A multiprofessional partners board inclusive of patient groups and NHS management governs the NCC-CC.

NCC-CC technical team

The technical team met approximately two weeks before each GDG meeting and comprised:

- the GDG group leader
- the GDG clinical advisor
- an information scientist
- a research fellow
- a health economist
- a project manager

[2] In April 2009 the NCC-CC merged with three other national collaborating centres, to form the National Clinical Guideline Centre (NCGC)

- administrative personnel.

Guideline Development Group

The GDG met monthly for 15 months (2004 to 2005) and comprised a multidisciplinary team of professionals, service users, carers and user organisation representatives who were supported by the technical team.

The GDG membership details including patient representation and professional groups are detailed in the GDG membership section in appendix M

(Members of the GDG declared any interests in accordance with the NICE technical manual. A register is available from the NCC-CC for inspection upon request (**ncc-cc@rcplondon.ac.uk**).) (enquiries@ncgc.ac.uk/).

Guideline Project Executive

The Project Executive was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope.

The Project Executive comprised:

- the NCC-CC director
- the NCC-CC manager
- an NCC-CC senior research fellow
- the NICE commissioning manager
- the technical team.

Sign-off workshop

At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

2.7 The process of guideline development

There are nine basic steps in the process of developing a guideline.

2006

First step: Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions. See Appendix A for details of the questions.

Second step: Systematically searching for the evidence

The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. Conference paper abstracts and non-English language papers were excluded from the searches. The research fellow identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See Appendix A for literature search details.

Third step: Critically appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general no formal contact was made with authors however there were *ad hoc* occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the Technical Manual{1}
- NCC-CC Quality Assurance document & Systematic Review paper available at (http://www.ncgc.ac.uk)

2006

Fourth step: Distilling and synthesising the evidence and writing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations.

Evidence tables are available at www.rcplondon.ac.uk/pubs/books/TB/index.asp

Fifth step: Grading the evidence statements and recommendations

The evidence statements and recommendations were graded in accordance with Table 2. The level of evidence and classification of recommendations were also included for diagnostic studies.

Table 2: Hierarchy of evidence and recommendation classification

Levels of evidence		**Classification of recommendations**	
Level	**Type of evidence**	**Class**	**Evidence**
1++	High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.	A	Level 1++ and directly applicable to the target population *or* level 1+ and directly applicable to the target population **AND** consistency of results. Evidence from NICE technology appraisal.
1+	Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias.		
1−	MA, SR of RCTs, or RCTs with a high risk of bias.	Not used as a basis for making a recommendation.	
2++	High-quality SR of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.	B	Level 2++, directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from 1++ or 1+.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.		
2−	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Not used as a basis for making a recommendation.	
3	Non-analytic studies (for example case reports, case series).	C	Level 2+, directly applicable to the target population and demonstrating overall

			consistency of results *or* extrapolated evidence from 2++.
4	Expert opinion, formal consensus.	D	Level 3 or 4 *or* extrapolated from 2+ *or* formal consensus *or* extrapolated from level 2 clinical evidence supplemented with health economic modelling.
		D (GPP)	A good practice point (GPP) is a recommendation based on the experience of the GDG.
Diagnostic study level of evidence and classification of recommendation was also included.			

Sixth step: Health economic evidence

Due to the appointment of the health economist midway through the guideline development, the areas for health economic modelling were considered after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they also commented on subsequent revisions.

Seventh step: Agreeing the recommendations

The sign-off workshop employed formal consensus techniques{1} to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The sign-off workshop also reached agreement on the following:

- seven key priorities for implementation
- eight key research recommendations
- five algorithms.

In prioritising key recommendations for implementation, the sign-off workshop also took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

The audit criteria provide suggestions of areas for audit in line with the key recommendations for implementation.

Eighth step: Structure of the full version of the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and is described below:

The clinical introduction sets a succinct background and describes the current clinical context.

The methodological introduction describes any issues or limitations that were apparent when reading the evidence base.

Evidence statements provide a synthesis of the evidence base and usually describe what the evidence showed in relation to the outcomes of interest.

Health economics presents an overview of the cost-effectiveness evidence base of relevance to the area under address.

'From evidence to recommendations' highlights the debate of the GDG. This section sets out the GDG decision-making rationale, providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.

The recommendations section provides stand-alone, action-orientated recommendations.

Evidence tables are not published as part of the full guideline but are available online at www.rcplondon.ac.uk/pubs/books/TB/index.asp. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

Ninth step: Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accord with the decision of the GDG. The guideline was then submitted for two formal rounds of public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed at the NICE website (www.nice.org.uk). Editorial responsibility for the full guideline rests with the GDG7.

Table 3 describes the various versions of the guideline that are available.

Table 3: Versions of this guideline

Versions	Comments
Full version	Details the recommendations. The supporting evidence base and the expert considerations of the GDG. Available at www.rcplondon.ac.uk/pubs/books/TB/index.asp
NICE version	Documents the recommendations without any supporting evidence. Available at www.nice.org.uk/page.aspx?o=guidelines.completed
Quick reference guide	An abridged version. Available at www.nice.org.uk/page.aspx?o=guidelines.completed
Information for the public	A lay version of the guideline recommendations. Available at www.nice.org.uk/page.aspx?o=guidelines.completed

2.8 Healthcare needs assessment

In contrast to many NICE guidelines, the scope requires service guidance in the prevention and control chapters of this guideline (chapters 11–13) and for rapid diagnostic techniques (sections 5.3 and 5.4). The NCC-CC conducted a rapid and simple healthcare needs assessment in order to establish current practice and resources, and to identify areas where these did not match the clinical need. This collected information through a review of the epidemiology of TB in England and Wales, and a review of current service by questionnaire among a sample of TB service providers.

Review of epidemiology

At the outset of the guideline development the prevention and control research fellow, Dr Ian Lockhart, compiled epidemiological data relevant to England and Wales from a number of national sources into a report to inform GDG discussions. This was refined through discussion at GDG meetings, is presented in this guideline in the Appendix G and in section 4.2, and will be described in a forthcoming paper.

Survey of current services

The NCC-CC sought information on current service provision in terms of staffing, location of specific services and caseload. Dr Sooria Balasegaram coordinated this survey through TB nurses and the Health Protection Agency's local and regional services. Further details are given in section 4.2 and will be described in a forthcoming paper.

2006

2.9 Funding

The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

2.10 Methodology – 2011

The Department of Health formally asked NICE to produce a short clinical guideline on interferon-gamma testing for diagnosing latent TB.

The following population subgroups were considered:

- Adults, young people and children at increased risk of infection by Mycobacterium tuberculosis complex (M. tuberculosis, M. africanum, M. bovis), specifically if they:
  - have arrived or returned from high-prevalence countries within the last 5 years
  - were born in high-prevalence countries
  - live with people diagnosed with active TB
  - have close contact with people diagnosed with active TB, for example at school or work

New 2011

  - are homeless or problem drug users
  - are, or have recently been, in prison.
- Adults and children who are immunocompromised because of:
  - prolonged steroid use (equivalent to 15 mg prednisolone daily for at least 1 month)
  - TNF-α antagonists such as infliximab and etanercept
  - anti-rejection drugs such as cyclosporin, various cytotoxic treatments and some treatments for inflammatory bowel disease, such as azathioprine
  - the use of immunosuppressive drugs
  - comorbid states affecting the immune system, for example HIV, chronic renal disease, many haematological and solid cancers, and diabetes.

New 2011

The updated sections of this guideline were developed in accordance with the process for short clinical guidelines set out in 'The guidelines manual' (2009) (see www.nice.org.uk/GuidelinesManual). There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/HowWeWork). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

2.11 Partial update scope

The guideline was developed in accordance with a specified scope, which detailed the remit of the guideline originating from the Department of Health (DH) and specified those aspects of TB to be included and excluded.

Before development of the guideline began, the scope was subjected to stakeholder consultation. The scope is given in Appendix F

2.12 Partial update Guideline Development Group

The GDG met every 6 weeks over a 5-month period from February until June 2010. The group comprised a multidisciplinary team of professionals, patients and carers who were supported by the technical team.

The GDG membership details can be found in appendix N.

Members of the GDG declared any interests in accordance with the NICE guidelines manual. These can be found in appendix N.

2.13 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

For the sections published in 2006 literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 30 November 2004 to be considered. For the section on the diagnosis of latent TB published in 2011 literature searches were not repeated because the development process was only a few months long. The section on diagnosing latent TB includes relevant papers published up until December 2009.

New 2011

Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

2006

The British National Formulary (BNF){5} should be consulted alongside any drug recommendations cited in this guideline and note taken of the indications, contraindications, cautions and product characteristics.

NICE guidelines will normally only make drug recommendations that fall within licensed indications. If a drug is recommended outside of its licensed indication this will be made clear in the guideline. This guideline contains recommendations for prescribing the following, all of which are within current licensed indications:

- ethambutol, for treating active tuberculosis
- isoniazid, for treating both latent and active tuberculosis
- pyrazinamide, for treating active tuberculosis
- rifampicin, for treating both latent and active tuberculosis
- streptomycin, for treating isoniazid mono-resistant active TB
- any glucocorticoid, for treating inflammation associated with active tuberculosis of the meninges or central nervous system (CNS).

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2006

3 Key messages of the guideline

3.1 Key priorities for implementation

A six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol) should be used to treat active respiratory TB[3] in:

- adults not known to be HIV positive A
- adults who are HIV positive B
- children. B

This regimen is referred to as the 'standard recommended regimen' in this guideline.

Patients with active meningeal TB should be offered:

- a treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (for example, ethambutol) for the first two months, followed by isoniazid and rifampicin for the rest of the treatment period D(GPP)
- a glucocorticoid at the normal dose range
  – adults: equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg A
  – children: equivalent to prednisolone 1–2 mg/kg, maximum 40 mg D(GPP)

with gradual withdrawal of the glucocorticoid considered, starting within 2–3 weeks of initiation.

Use of directly observed therapy (DOT) is not usually necessary in the management of most cases of active TB. A

All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular:

[3] TB affecting the lungs, pleural cavity, mediastinal lymph nodes or larynx.

- street- or shelter-dwelling homeless people with active TB B
- patients with likely poor adherence, in particular those who have a history of non-adherence. D(GPP)

The TB service should tell each person with TB who their named key worker is, and how to contact them. This key worker should facilitate education and involvement of the person with TB in achieving adherence. D(GPP)

New entrants[4] should be identified for TB screening from the following information:

- port of arrival reports D(GPP)
- new registrations with primary care B
- entry to education (including universities) D(GPP)
- links with statutory and voluntary groups working with new entrants. D(GPP)

Neonatal Bacille Calmette-Guèrin (BCG) vaccination for any baby at increased risk of TB should be discussed with the parents or legal guardian. D(GPP)

Primary care organisations with a high incidence of TB[5] should consider vaccinating all neonates soon after birth. D(GPP)

2006

[4] New entrants are defined as people who have recently arrived in or returned to the UK from high-incidence countries, with an incidence of more than 40 per 100,000 per year, as listed by the Health Protection Agency (go to www.hpa.org.uk and search for 'WHO country data TB').
[5] Incidence of more than 40 per 100,000, as listed by the Health Protection Agency; go to www.hpa.org.uk and search for 'tTB rate bands'

3.2 Algorithms

2006

The following algorithms appear in this document:

- algorithm showing isolation decisions for patients with suspected TB (*see* Figure 2)
- algorithm for testing and treating asymptomatic children aged between four weeks and two years old who are contacts of people with sputum smear-positive TB (*see* Figure 10)
- algorithm for asymptomatic household and other close contacts of all cases of active TB (*see* Figure 11).
- algorithm for new entrant screening (*see* Figure 12)
- algorithm for new NHS employees (*see* Figure 13).

3.3 Audit criteria

Table 4: Audit criteria

Key priority for implementation	Criteria	Exception	Definition of terms
A six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol) should be used to treat active respiratory TB in: • adults not known to be HIV positive A • adults who are HIV positive B • children. B This regimen is referred to as 'standard recommended regimen' in this guideline.	a) Process measure: percentage of patients with active TB receiving rifampicin, isoniazid, pyrazinamide and ethambutol (or other fourth drug) for the first two months of treatment. b) Outcome measure: percent cure and completion rate.	Contraindications, meningeal TB, CNS involvement, drug resistance.	
Patients with active meningeal TB should be offered:	a) Process measure: percentage of	Contraindications, drug resistance.	b) Any patient who received glucocorticoids for

2006

• a treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (for example, ethambutol) for the first two months, followed by isoniazid and rifampicin for the rest of the treatment period D(GPP) • a glucocorticoid at the normal dose range • adults – equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg A • children – equivalent to prednisolone 1–2 mg/kg, maximum 40 mg D(GPP) with gradual withdrawal of the glucocorticoid considered, starting within two to three weeks of initiation.	patients with meningeal TB receiving rifampicin, isoniazid, pyrazinamide and ethambutol (or other fourth drug) for the first two months of treatment. b) Process measure: percent receiving/having received glucocorticoids. c) Outcome measure: percent cure and completion rate (12 months).		at least two weeks.	2006

Use of DOT is not usually necessary in the management of most cases of active TB. A All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular: a) street- or shelter-dwelling homeless people with active TB B b) patients with likely poor adherence, in particular those who have a history of non-adherence. D(GPP)	Process measure: percentage of patients with active TB who are treated with DOT.		A 'patient on DOT' is any patient who has been prescribed anti-TB drugs as directly observed therapy (regardless of observer) for part or all of their treatment.	2006
The TB service should tell each person with TB who their named key worker is, and how to contact them. This key worker should facilitate education and involvement of the person with TB in achieving adherence. D(GPP)	Process measure: percentage of TB patients in possession of current correct key worker's details.	Hospital inpatients.	Key worker will have been named as specified in recommendations.	

New entrants should be identified for TB screening from the following information: • port of arrival reports D(GPP) • new registrations with primary care B • entry to education (including universities) D(GPP) • links with statutory and voluntary groups working with new entrants. D(GPP)	a) Process measure: percentage of new entrants referred or recorded who are contacted for screening. b) Process measure: percent of new entrants contacted for screening, who complete the screening. c) Process measure: percent of new entrants contacted for screening, who are referred to secondary care TB teams.	a) Any people sought but not found. b) Any people sought but not found. Loss to follow-up, including not returning for Mantoux test to be read, chest X-ray to be taken, treatment for latent TB infection to be started, etc.	b) Any person who completes the screening process according to the algorithm is counted.	2006

Neonatal BCG vaccination for any baby at increased risk of TB should be discussed with the parents or legal guardian. D(GPP) Primary care organisations with a high incidence of TB[6] should consider vaccinating all neonates soon after birth. D(GPP)	a) Process measure: percentage of neonates vaccinated with BCG. b) Process measure: percentage of eligible neonates vaccinated with BCG.	Informed refusal, HIV.	2006

[6] As defined by the Health Protection Agency; go to www.hpa.org.uk and search for 'tuberculosis rate bands'

4 Aims and principles of tuberculosis care

In 2005, the Chief Medical Officer's TB Action Plan, *Stopping tuberculosis in England,*{2} set out essential tasks for reversing the increase in tuberculosis incidence and ensuring high-quality care and public health. The very first task in the action plan is the production and wide availability of information and educational materials on tuberculosis, and it specifies that they should be 'multi-lingual and culturally appropriate'. The GDG enthusiastically support this, and therefore this guideline recommends the availability of such information and materials throughout the NHS, tailored to meet the needs of different languages and cultures.

As part of the action for 'excellence in clinical care', the action plan calls for a named key worker assigned to every patient, and that they should work closely with other agencies such as housing and social services to achieve improved outcomes. The GDG acknowledged the great importance of achieving a care plan which makes the successful completion of treatment of active or latent TB as easy as possible for the person receiving the treatment, and so this guideline has provided recommendations to support these aims and those of the Chief Medical Officer.

Where scientific evidence supports it, the parts of this guideline addressing prevention and control (chapters 11–13) include recommendations for aspects of service organisation as well as for individual teams of healthcare professionals. The guideline attempts to focus NHS resources where they will effectively combat the spread of TB, and in some sections deals with high- and low-incidence areas separately.

The GDG acknowledge the importance of honest and positive communication concerning TB in overcoming stigma, poor concordance and misinformation about the condition and recognising socio-economic factors. Healthcare teams caring for people with, or at risk from, TB will need to work with non-NHS agencies to ensure a seamless service that promotes detection, concordance and cure.

2006

4.1 Current service organisation

The review of current services (see Appendix G for more details) identified four basic service models in use.

Centralised

In this model TB nurses are based in a central unit, usually the health protection unit (HPU), and are responsible for all TB services including contact tracing and screening in a defined area. This model is used in areas with high and low incidence. It allows all TB services in the area to be coordinated and standardised. A variant which resembles the specialist hospital-based model (see below) is seen in some low-incidence small geographical areas, where a few nurses based in local hospitals or community clinics can achieve high volumes of specialisation.

Central with satellites

This is a variation of the first model; there are nurses at HPU level and other clinics alongside such as specialist new entrant and screening clinics. It may include generalist clinics in hospitals. In some cases the HPU nurse may coordinate all TB services, including contact tracing using satellite clinics. In this model, the HPU nurse may identify and send individuals for contact tracing to non-specialist health visitors in the community. It allows for coordination of services in areas of large geographical distance.

General hospital/community model

General respiratory nurses see people with TB in this model, sometimes with an additional nurse led clinic for contact tracing, BCG or new entrant screening. This model is used in areas of lowest incidence. Nurses may also be based in the community, and may run screening clinics.

Specialist hospital-based model

TB nurses are based in clinics in local hospitals or specialist community screening units but have functions for the surrounding community. There may a larger HPU-based network connecting these nurses. This model is seen in London and other areas with a relatively high TB incidence.

Staffing levels

The review aggregated staffing levels across HPUs to account for apparent imbalances between different types of clinic within each local area. The scatter plot of notifications against whole time equivalent (WTE) nursing staff (Figure 1) shows a clear correlation (Spearman's ρ =0.85), which is perhaps an indication that services are now in line with the British Thoracic Society (BTS) code of practice's{6} recommendations. These stated that nursing staff should be maintained at one WTE nurse (or health visitor) per 50 notifications per year outside London, and 40 per year in London. The review reflects a development in TB services since the audit conducted in 1999.{7} However, notification rates continue to increase in England and Wales, and it would seem that the challenge for those planning TB services is to see this increase in resources targeted effectively at those activities for which the evidence demonstrates benefit. This guideline aims to inform those decisions wherever possible.

Across HPUs, the WTE rate is roughly 1 per 40 notifications. London HPUs have the highest caseload and hence the highest WTE.

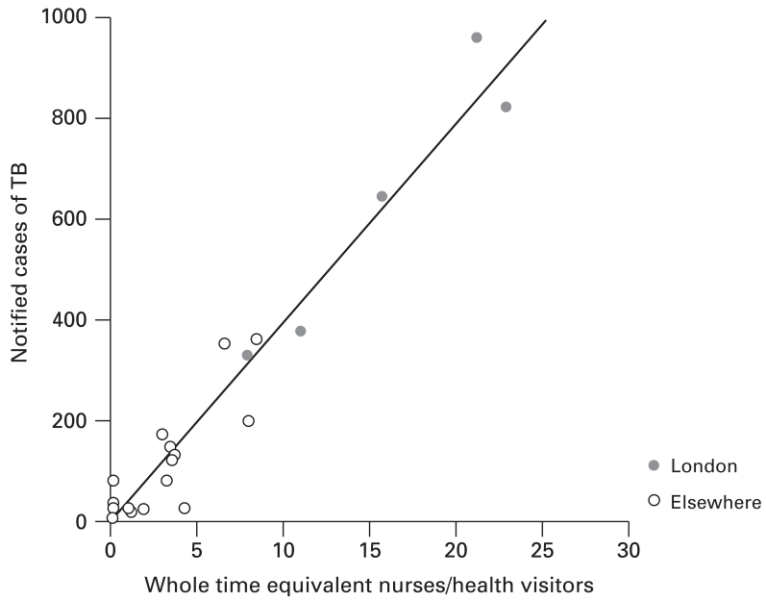


Figure 1: Staffing levels of nurses/health visitors vs notified cases of TB. The line represents one whole time equivalent per 40 cases

2006

Other information on current services

The following aspects of the review of current services are reported in this guideline (details of the methods employed are given in Appendix G):

- dedicated TB clinics (section 6.1)
- nurse-led follow-up clinics (section 6.1)
- specialist HIV/TB clinics (section 6.1)
- specialist paediatric TB clinics (section 6.1)
- directly Observed Therapy (DOT) (section 8.2)
- free prescriptions (section 8.3)
- measures to improve adherence (section 8.3)
- outreach (section 8.3)
- incentives for attending clinic (section 8.3)
- treatment of latent TB infection (sections 10.2 and 12.2)
- negative pressure facilities (section 9.3)
- BCG clinics (section 11)
- neonatal BCG (section 11.1)
- high risk group screening (section 12)
- contact tracing clinics (section 12.2)
- *Mycobacterium bovis* (section 12.3)
- specialist new entrants clinics (section 12.7)
- prison services (section 13.3).

4.2 Communication and patient information

During the development of the guideline, patient and carer representatives on the GDG highlighted these suggestions:

- a single national source of high-quality TB information in relevant languages, and formats for vision- or hearing-impaired people
- TB services to assess local language and other communication needs, and accordingly make information from the national source available locally

- clear discussion between healthcare professionals, people with (or at risk from) TB and their carers about tests, treatment, contact tracing and infection control measures, to enable understanding
- people with both HIV and TB to be provided with information about the different specialties who may provide care during and after their treatment for TB
- contact tracing explained and handled sensitively to avoid misunderstanding and stigma
- information set out so as not to medicalise the patient
- TB services providing each patient completing anti-tuberculosis treatment with clear 'inform and advise' information

The first task for improving TB services to be named in the Chief Medical Officer's TB Action Plan{2} is to 'produce multilingual and culturally appropriate public information and education materials for national and local use and make them widely available'. See also section 2.5 above, for details of the National Knowledge Service.

Communication and information provision are an important part of efforts to successfully reverse the increase in TB incidence in England and Wales. Information resources for TB address the following aims:

- achieving earlier diagnosis through general public awareness of symptoms
- combating stigma and myths, which may delay presentation and impede contact tracing
- helping to achieve concordance and treatment completion through awareness of different treatment options, awareness of side effects, and the importance of adhering to the treatment regimen
- relieving anxiety about infection control measures in healthcare settings, family life and the workplace.

Recommendations are therefore given under section 6.2.

2006

4.3 HIV co-infection

2006

This guideline discusses risk assessments for HIV, and gives recommendations for treatment of active and latent TB in co-infected people. However, the specialised guidelines in the UK, at the time of going to press, are those from the British HIV Association,{8} and readers should be aware of these when considering care of any patient who is known to be, or is possibly, co-infected.

The Guideline: Diagnosis and Treatment

5 Diagnosis

5.1 Diagnosing latent tuberculosis

5.1.1 Clinical introduction

In asymptomatic persons exposure to, and potential infection with, tuberculosis is demonstrated by a positive skin test, or more recently from a positive blood-based immunological (interferon-gamma) test. Those with a strongly positive skin test are then regarded as having been infected with tuberculosis. Of these people presumed infected, there is a 10–15% chance of developing clinical disease at some point in their lives. If a co-morbidity develops which reduces the immune system (see section 10.2), that risk is increased. The majority of exposed persons will kill off the inhaled bacteria, and be left only with a positive skin test as a marker of exposure. About half of those who develop the clinical disease will do so within five years of the initial infection. In cases where a long period elapses between infection and development of disease, dormant bacilli are thought to remain in either the lung or other sites, which can 'reactivate' in favourable circumstances for the organism.

Until recently, only Mantoux tests were available to give evidence of exposure. The tuberculin tests had the advantage of being cheap and relatively easy to perform, but suffered from a number of problems. The test results have to be interpreted within a certain timescale, and patients who do not return, or delay returning, will have either no result or a possibly inaccurate one. False positive results can occur because of the sensitising effect on the immune system of either prior BCG vaccination or opportunist environmental mycobacteria. False negative results can occur due to anything reducing immunity, particularly co-infection with HIV, but also treatments such as cytotoxics, or immunosuppression. Extensive tuberculosis (pulmonary or miliary) can itself also temporarily depress the immunity, and can lead to a paradoxically negative Mantoux tests. More recently, selective immunological

(interferon-gamma) tests have been developed using the tuberculosis antigens 'early secretion antigen target 6′ (ESAT-6) , 'culture filtrate protein 10′ (CFP-10) and tb7.7, which are not present in BCG, and are found in only a few species of environmental mycobacteria. These can be done on either cells or cell products derived from whole blood tests. These tests aim to be more specific by removing false positive results, and to be better correlated with latent infection or dormant organisms.

2006

5.1.2 Methodological introduction

2006, amended 2011

Because there is now additional evidence available on the use of IGT, the partial update of CG33 sought to make recommendations on the use of IGT for diagnosis of latent TB.

There are currently three interferon-gamma immunological tests commercially available for use in the UK: QuantiFERON-TB Gold, QuantiFERON-TB Gold In tube and T-SPOT.*TB*. QuantiFERON-TB Gold measures the release of interferon-gamma in whole blood in response to stimulation by ESAT-6 and CFP-10 which are not present in BCG vaccine strains or the vast majority of non-TB mycobacteria. The In tube version measures ESAT-6, CFP-10 and tb7.7 In the T-SPOT.*TB* test, individual activated ESAT-6 and CFP-10 specific T-cells are enumerated using ELISPOT methodology

In order to make appropriate recommendations, review questions were framed according to the following population groups: adults young people and children from high incidence countries, adults, young people and children who had been in contact with individuals with active TB, or immunocompromised individuals. Children were treated as a separate population because they have a less developed immune system than adults, and the mechanism of action of the tests relies on a fully developed immune system.

The key clinical questions considered were:

1. Which diagnostic strategy is most accurate in diagnosing latent TB in adults, young people and children who are recent arrivals from high prevalence countries?

2. Which diagnostic strategy is most accurate in diagnosing latent TB in children?

3. Which diagnostic strategy is most accurate in diagnosing latent TB in adults, young people and children (children considered as a separate population) who have been in close contact with patients with active TB?

4. Which diagnostic strategy is most accurate in diagnosing latent TB in immunocompromised patients?

5. What is the effectiveness of screening using IGT for healthcare workers?

The review protocol is included in appendix B.

A search strategy was used which aimed to identify relevant studies for all the review questions. The following databases were searched: Cochrane database of systematic reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health technology assessment (HTA) database, Medline, Embase, Cinahl, NHS Economic Evaluation database (NHS EED). Trial registers such as Cochrane central register of controlled trials (CENTRAL), UKCRN Portfolio database, current controlled trials, clinicaltrials.gov were searched. Websites of relevant organisations such as World Health Organisation and TB alert were also searched. No methodology search filters or publication date filters were used. A total of 5270 studies were identified for the whole review. After sifting by abstract, 467 studies were selected (n = 56, 70, 69 ,153 and 5 for questions 1 to 5 respectively).

Studies were excluded if they**:**

- did not compare Mantoux tests with IGT
- evaluated IGT based on purified protein derivative
- did not focus on latent TB
- focused on treatment of TB
- focused on non commercial IGT or in-house IGT.

The detailed evidence tables for the included studies and list of excluded papers and reasons for exclusion are given in appendices O and J.

There were methodological issues with the included papers. For example, active TB was not always excluded (either through investigation or not reported), there was repeated testing of both Mantoux and IGTs, the threshold for positive Mantoux tests varied, and it was not clear whether the use of cut-offs was always age appropriate. If identified, these issues were used to downgrade the quality of the evidence in the GRADE tables.

Diagnostic accuracy studies considered as high quality are those where the index test(s) are compared with a recognised, validated reference standard. Measures of accuracy, when compared with the reference test, such as sensitivity and specificity can then be determined. The Mantoux test has been the preferred test in clinical practice for several years but it is not an ideal reference standard; for example, the specificity of the Mantoux test is confounded by BCG vaccination. This implies false-positive results could be seen in this group of people because the Mantoux test is not able to distinguish between individuals who actually have the infection, and those who have been vaccinated with BCG. Because of such concerns about the Mantoux test as a reference standard, other measures of effect such as discordance, concordance and odds ratios are used. These measure the association between the results of the test(s) and the risk of having latent TB, but do not give any information on rates of false positives or negatives.

In addition, the GRADE methodology has not been fully developed for diagnostic studies. A modified form of GRADE was used to assess the quality of evidence found. Standard GRADE profiles for interventions use the following criteria to assess quality of evidence: limitations, inconsistency, imprecision and indirectness. In this review the same criteria were applied. Footnotes have been included to define and describe what the criteria mean in the context in which the studies were analysed. It was not possible to measure imprecision so this has been noted as ‘not measurable’ in the tables. This is because guidance has not yet been developed to address thresholds for imprecision for the measures of effect that were determined. These

measures of effect did not appropriately describe the effectiveness of the diagnostic tools. Therefore, the GDG were not asked to agree a pre-defined threshold for imprecision. For questions on children and contact tracing it was possible to pool the ratio of odds ratios and to perform a meta analysis. The ratio of odds ratios is a measure of effect which reflects test performance and provides an approach to evaluating tests in the absence of a reference test. The odds ratio (OR) is a function of test sensitivity and specificity and increases as one or both of these measures increase. Statistically OR = [sensitivity/(1-specificity)]/[(1-sensitivity)/specificity].

The spreadsheets used to calculate and determine the risk categories as defined by level of exposure to active TB are given in appendices P and Q.

The main aim of this update was to review diagnosis of latent TB using tests for which there is no ideal reference standard for comparison. One important objective was to identify appropriate measures of effect to assess the diagnostic utility of the tests. Different approaches were taken to address this objective.

- Discordance and concordance between the IGT and Mantoux tests were measured in some of the papers. There were few prospective studies to identify participants who would either develop active TB following a positive test result or stay healthy following a negative test result. These studies are designed to determine positive and negative predictive values. For diagnosis of latent TB this type of design would give the most accurate prognosis predicting those who will get active TB and those who would not.
- In other studies the odds of a positive test associated with graded exposure to an active TB case were measured. In these cases a proxy measure of effect, the ratio of odds ratios could be calculated if figures of positive test results of study participants were clearly stated, and where the exposure status of those participants had been identified. The main disadvantage of this proxy measure is that it fails to identify whether the good performance of a test compared with another is because of either

better sensitivity, specificity or both. It is impossible therefore to determine the false positive and false negative rates of a particular test.

5.1.3 Partial update health economics introduction

The following sections outline the updated modelling for two populations identified in the scope: adult contacts (including health care workers) and screening people from high prevalence countries. However, because of an absence of evidence, no cost-effectiveness analysis was conducted for all child and young people populations. Because of an absence of information no new distinct analysis was conducted for screening new NHS employees and the immunocompromised population. For children, the almost complete absence of sensitivity and specificity information and quality of life data meant that a useful analysis could not be produced. For the two remaining adult populations the results of the other two analyses will be extrapolated to these situations

A search for cost-effectiveness studies identified five relevant papers that examined the use of IGT in screening people from high prevalence countries with suspected latent TB infection, and one relevant paper that examined the use of IGT in the adult contacts and healthcare workers contacts with suspected latent TB infection. The papers were reviewed with quality checklists to assess their applicability and limitations. A completed checklist is available in annex 6 in appendix L. None of the papers were considered applicable to the decision problem either because they were not based in the UK or did not include consideration of quality of life. However cost-effectiveness papers were used to explore approaches to modelling strategies and to inform the structure of the model.

A decision model based on the previous guideline was used to compare the expected cost effectiveness of four strategies of testing for latent infection in both adult (aged more than 18 years) populations described above. The strategies compared were:

- Mantoux test

- IGT
- Mantoux test followed by IGT
- no test.

In the model, treatment follows current policy; with appropriate therapy for people diagnosed with active and latent TB. The analysis did not compare different types of skin tests or IGTs because this was outside the scope of this guideline.

The key areas that were updated were the test accuracies and the relevant costs. All costs were updated to current prices and were validated by the GDG. The test accuracies were based on published reviews which calculated sensitivities and specificities again after validation by the GDG.

The assumptions made in the initial guideline were still applicable unless stated otherwise. Whenever possible, input parameters and assumptions were based on empirical evidence, but some key parameters were estimated by the health economist and GDG. The model considers the quality-adjusted life years (QALYs) lost because of infection, adverse events and developing TB. Therefore, the interventions with the smallest QALY loss are the most effective. Throughout the analysis incremental cost-effectiveness ratios (ICERs) will be compared with a common base line (usually no test) and net monetary benefits will be calculated. Net monetary benefit quantifies which treatment option provides the greatest health benefit for a given threshold. A threshold of £20,000 per QALY gained was used in this analysis. Probabilistic sensitivity analysis was considered, however some of the estimates of the means of variables were assumptions and it was therefore considered more instructive to do a series of one way sensitivity analysis rather than a probabilistic sensitivity analysis.

For each population details were given on the source of the new test accuracy data with base-case results and sensitivity analyses.

5.1.4 Diagnosis of latent TB in people who are recent arrivals from countries where TB is highly prevalent

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent TB in adults and children who are recent arrivals from highly prevalent countries?

Evidence review

Of the ten studies included:

- three were conducted in Germany (Diel et al. 2006; Diel et al. 2008; (Anon)
- two in the Netherlands (Franken et al. 2007; Kik et al. 2009)
- two in the United States (Brodie et al. 2008; Porsa et al. 2006)
- one in Italy (Carvalho et al. 2007)
- one in Norway (Winje et al. 2008)
- one in Switzerland (Janssens et al. 2008).

All studies looked at participants from high prevalence countries from places such as sub Saharan Africa, Central and South America, Eastern Europe and Asia.

The main measures of effect used were:

- concordance and discordance between tests
- agreement between the tests as measured by kappa values
- odds ratios

- ratio of odds ratios (ROR). In this guideline ROR is mathematically defined as (odds of positive IGT in a high-risk area divided by the odds of a positive test in a low-risk area) divided by (odds of a positive Mantoux test in a high-risk area divided by a positive Mantoux test in a low-risk area)

Table 5 Diagnosis of latent TB infection in foreign-born people and in people arriving from high-prevalence countries

Study[1]	Population group (by prevalence or place of birth or racial group)	Odds ratio (Mantoux test ≥ 5 mm)	Odds ratio (Mantoux test ≥ 10 mm)	Odds ratio (Mantoux test ≥ 15 mm)	Odds ratio (IGT)	ROR	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality	2006, amended 2011
Janssens et al. (2008)	< 50 per 100,000	1	1	–	1	–	Y	Y	N	-	N	Low	
	50–99 per 100,000	2.58 (1.26 to 5.27)	2.22 (1.15 to 4.27)	–	2.17 (1.13 to 4.15)	0.98							
	> 100 per 100,000	3.67 (1.40 to 9.60)	3.84 (1.61 to 9.20)	–	2.62 (1.18 to 5.82)	0.68							
Diel et al. (2008)	Germany	1	1	–	1	–	Y	N	N	-	N	Low	
	Not Germany	5.81 (3.6 to 9.1)	5.2 (3.2 to 8.4)	–	2.28 (1.3 to 3.9)	0.438							
Nienhaus et al. (2008)	Germany (< 6 per 100,000)	–	1	–	1	–	N	N	N	-	N	Low	
	Not Germany (> 20 per 100,000)	–	4.6 (3.21 to 6.53)	–	2.6 (1.71 to 4.09)	0.565							
Diel R et al. (2006)	Germany (< 6 per 100,000)	1	1	–	1	–	Y	N	N	-	N	Low	
	Not Germany (> 20 per 100,000)	5.4 (2.7 to 10.6)	7.3 (3.7 to 14.3)	–	4.7 (2.1 to 10.5)	0.644							
Porsa et al. (2006)	USA (< 10 per 100,000)	–	1	–	1	–	Y	N	N	-	N	Low	
	Not USA (25–300 per 100,000)	–	20.20 (4.21 to 79.02)	–	2.86 (0.67 to 12.15)	0.141							

Study[1]	Population group (by prevalence or place of birth or racial group)	Odds ratio (95%CI) Mantoux test ≥ 5 mm	Odds ratio (95%CI) Mantoux test ≥ 10 mm	Odds ratio (95%CI) Mantoux test ≥ 15 mm	Odds ratio (95%CI) IGT	ROR	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Kik et al. (2009)	Asia		1		1		Y	N	Y	-	N	Low
	Europe, North America		1.69 (0.44 to 6.45)		QFT = 0.48(0.17 to 1.36); TSPOT = 0.35(0.13 to 0.99)							
	Sub-Saharan Africa		6.00 (1.32 to 27.24)		QFT = 2.97 (1.40 to 6.27); TSPOT 2.40 (1.13 to 5.10)							
Winje et al. (2008)	Asia			1	1		Y	N	Y	-	N	Low
	Europe			2.7 (1.5 to 4.9)	1.0 (0.6 to 1.6)							
	Africa			3.8 (2.4 to 5.8)	3.1 (2.2 to 4.2)	0.82						
Porsa et al. (2006)	CaucasianWhite		1		1		Y	N	N	-	N	Low
	African-Caribbean		4.97 (1.58 to 15.68)		5.57 (1.16 to 26.74)	1.12						

[1] Outcomes were diagnostic utility and threshold value for a positive diagnosis of latent TB.

[2] Odds Ratio for a positive test in people who are foreign-born or from high endemic areas adjusted for BCG vaccination, age, gender and exposure time.

Limitations were the lack of a reference test means the measures of effect of sensitivity and specificity cannot be determined. Inconsistencies were different studies used different types of Mantoux test. Imprecision was not measurable.

CI = confidence interval. IGT = inferferon gamma test. ROR = ratio of odds ratios. QFT = QuantiFERON-TB interferon gamma test. TB = tuberculosis. TSPOT = T-SPOT.TB interferon gamma test

2006, amended 2011

	OVERALL						BCG VACCINATED						NON BCG VACCINATED												2006, amended 2011
	Induration						Induration						Induration						Limitations	Inconsistensy	Indirectness	Imprecision	Other Considerations	Quality	
Studies	5 mm		10 mm		15 mm		5 mm		10 mm		15 mm		5 mm		10 mm		15 mm								
	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa	Concordance	kappa							
Porsa et al. 2006	90 %(87–93 %)	0.25(0.1–0.41)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Y	N	N	-	N	very low	
Franken et al. 2007	ND	ND	82%	0.19	92.30 %	0.24	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Y	N	N	-	N	very low	
Carvalho et al. 2007	ND	ND	71%	0.37	ND	ND	ND	ND	0.28(0.10–0.77)a OR	ND	ND	ND	ND	ND	ND	ND	ND	ND	Y	N	N	-	N	Low	
Brodie et al. 2008	64 %(54–74 %)	0.33 (0.19–0.48)	ND	ND	ND	ND	56% (43–68)	0.22 (0.06–0.37)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Y	N	Y	-	Y	very low	

Janssens et al. 2008	60.70 %	0.24(0.14–0.33)	63.60%	0.27(0.16–0.38)	63.90 %	0.19(0.09–0.30)	ND	ND	ND	ND	ND	ND	78.40 %	0.47(0.20–0.74)	76.50 %	0.41(0.14–0.68)	78.40 %	0.28(0.03–0.54)	N	N	N	-	Y	Low	2006, amended 2011
Nienhaus et al. 2008	74.80 %	0.26	84.20%	0.37	89.80 %	0.33	ND	0.12	ND	0.28	ND	ND	ND	0.5	ND	0.54	ND	0.3	N	N	N	-	Y	Low	
Diel et al. 2006	ND	ND	ND	ND	ND	ND	38.90%	0.08	77.10 %	0.35	ND	ND	89.50 %	0.58	94.10 %	0.68	ND	ND	N	N	N	-	Y	Low	
Winje et al. 2008	72 %	0.43(0.37–0.49)	79%	0.51(0.45–0.57)	78 %	0.39(0.32–0.47)	ND	ND	ND	0.45(0.37–0.52)	ND	ND	ND	ND	ND	0.66(0.56–0.77)	ND	ND	Y	N	N	-	Y	Low	
Diel et al. 2008	69.20 %	0.276	ND	ND	ND	ND	44.20%	0.119	ND	ND	ND	ND	90.70 %	0.616	ND	ND	ND	ND	Y	N	N	-	Y	low	

Table 6 Degree of concordance between Mantoux tests and IGT and corresponding threshold for Mantoux test

Evidence statements

Low quality evidence from four studies with 2646 participants showed that there was a higher level of concordance and agreement between IGT and Mantoux test when both tests were used in non-BCG-vaccinated populations than in populations who were BCG vaccinated.

Low quality evidence from three studies with 2351 participants showed that BCG vaccination decreased both concordance and agreement between the assay results of IGT and Mantoux tests.

Low quality evidence from one study showed IGTs were more likely to detect progression to active TB than Mantoux tests over a 2-year period. Positive predictive values were 14.6% and 2.3% respectively.

Low quality evidence from one study following up 339 immigrant contacts for a median of 1.83 years showed that IGT and Mantoux tests were similar in detecting progression to active TB. Positive predictive values were 3.1% and 3.8% for Mantoux test thresholds of 10 mm and 15 mm and 2.8% and 3.3% for QFT and T-SPOT. Negative predictive values for the Mantoux test thresholds of 10 mm and 15 mm, and QFT and TSPOT were 100%, 99.3%, 98% and 98.3% respectively.

Very low quality evidence from four studies with 1636 participants showed very low levels of concordance between the Mantoux and IGTs in BCG-vaccinated populations

Health economics – diagnosing latent TB in adults and children who are recent arrivals from high prevalence countries

The published reviews of test accuracy identified were Pai et al. (2008) and Diel et al. (2010). Both use active TB as a proxy for the calculation of sensitivities and specificities. Because there was no differentiation between IGTs, midpoints were used for the accuracy estimates.

The base-case analysis is shown in table 7. It used a prevalence of 30% for latent TB in the cohort group. These results demonstrate that Mantoux tests/IGT and IGT are associated with ICERs which are just under £30,000

per QALY. These estimates are within a range that means NICE requires further consideration of the various input parameters before a decision can be made.

Table 7 Cost-effectiveness results for new entrants from high prevalence countries

Strategy	Cost	Effect (QALY loss)	ICER per QALY gained compared with no test	Net monetary benefit (£20,000 per QALY)
Pai et al. 2008				
No test	£316	9.98686	-	-
Mantoux test/IGT	£403	9.99015	£26,641	−£22
IGT	£452	9.99156	£29,043	−£43
Mantoux test	£458	9.99107	Dominated	Dominated
Diel et al. 2010				
No test	£316	9.98686	-	-
Mantoux test/IGT	£387	9.98925	Extended dominance	Extended dominance
IGT	£451	9.98994	£29,211.57	−£43
Mantoux test	£442	9.99150	Extended dominance	Extended dominance

ICER = incremental cost-effectiveness ratio IGT = interferon gamma test. QALY = quality-adjusted life year.

A number of sensitivity analyses were run and are presented in appendix L. The prevalence of latent TB in this population and the transformation rate of latent TB to active TB are presented in tables 8 and 9 because the GDG considered them to be two of the key parameters in the model. The net monetary results at £20,000 per QALY are presented in table 8.

Table 8 Net monetary benefits at £20,000 per QALY gained for different prevalence rates and test accuracy sources for screening people from high prevalence countries

Prevalence	Mantoux test/IGT	IGT	Mantoux test
Pai et al. 2008			
0.01	−34	−73	Dominated
0.05	−32	−69	Dominated
0.1	−30	−64	Dominated
0.15	−28	−58	Dominated
0.2	−26	−53	Dominated
0.25	−24	−48	Dominated
0.3	−22	−43	Dominated
Diel et al. 2010			
0.01	−34	−74	Dominated
0.05	−33	−69	Dominated
0.1	−31	−64	Dominated
0.15	−30	−60	Dominated
0.2	−27	−53	Dominated
0.25	Extended Dominated	−48	Extended Dominated
0.3	Extended Dominated	−43	Extended Dominated
IGT = interferon gamma test. QALY = quality-adjusted life year.			

Table 9 Net monetary benefits at £20,000 per QALY gained for different transformation rates and test accuracy sources for screening people from high prevalence countries

Latent TB to active TB	Mantoux test/IGT	IGT	Mantoux test
Pai et al 2008			
0.01	-60	-97	Dominated
0.05	-9	-24	Dominated
0.1	55	66	Dominated
0.15	119	157	Dominated
0.2	183	247	Dominated
0.25	247	338	Dominated
0.3	311	428	Dominated
Diel et al 2010			
0.01	Extended dominance	-97	Extended dominance
0.05	Extended dominance	-15	Extended dominance
0.1	Extended dominance	67	Extended dominance
0.15	Extended dominance	149	Extended dominance
0.2	Extended	231	Extended

	dominance		dominance
0.25	Extended dominance	334	Extended dominance
0.3	Extended dominance	416	Extended dominance
IGT = interferon gamma test. QALY = quality-adjusted life year. TB = tuberculosis.			

These results suggest that as the prevalence of TB and the conversion rate of TB increase the tests (Mantoux test/IGT and IGT alone) will be cost effective. IGT appears to be the optimum choice based on cost effectiveness. However, the results indicate that relatively small differences in either the prevalence or the transformation rate could result in Mantoux test/IGT being the optimum choice. In addition, the deterministic ICER per QALY gained for Mantoux test/IGT suggests it is a cost-effective option.

Evidence to recommendations

The issue of generalisability of the studies to the UK population was raised as well as how the results could be applied to a UK setting. It was agreed that the studies had similar settings and prevalence figures to the UK. The GDG noted that IGT was being used in certain UK practices. The evidence presented was of low quality but it showed how a previous BCG vaccination would confound the Mantoux test results and not affect the IGT results. The GDG felt that good quality evidence to predict active TB in the future was required.

Evidence to recommendations – health economics (people who have arrived from high-prevalence countries)

Health economic analysis indicated that none of the tests were associated with ICERs of below £20,000 per QALY gained. However the GDG considered that the mean rate of transformation from latent TB to active TB was an underestimate and that the true rate was closer to 16% over 15 years; evidence from Kik et al. (2010) suggested equivalent rates of close to 3% over 2 years. At estimates this high, IGT alone is the most cost-effective option, followed by the Mantoux test/IGT dual strategy. The threashold for screening was reduced from 500/100,000 to 40/100,000 as the GDG considered this to be cost effective and provided the greatest health benefits. The GDG considered that while IGT alone appeared to be the most cost-effective option,

the dual strategy should remain as an alternative because there was significant uncertainty in the point estimates, it was a less expensive strategy that would be more effective in low incidence areas and, in particular, there were still issues over the operation of the tests and intersubject variability.

5.1.5 Diagnosis of latent TB in children

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent TB infection in children?

Evidence review

Of the 11 studies included:

- four were conducted in Asia (Chun et al. 2008, Higuchi et al. 2007, Higuchi et al. 2009, Okada et al. 2008), three in Europe (Brock et al. 2004, Hansted et al. 2009, Winje et al. 2008b), two in North America (Lighter et al. 2009, Tsiouris et al. 2006) and two in Australasia (Connell et al. 2006, Connell et al. 2008)
- ages ranged from 0 to 19 years
- grading of exposure differed between studies (for example, sleeping proximity, duration of exposure, contact type).

The studies also looked at other factors such as BCG vaccination and country of birth.

Exposure was measured in several ways:

- duration of contact
  - hours/day
  - hours/week
- sleeping proximity
  - same or different house
  - same or different room
- type of contact
  - household/close
  - non-household
  - unknown
  - school
  - casual.

2006, amended 2011

The following measures of effect were used:

- concordance between tests
- agreement between tests measured by kappa value
- risk factors for positive test result
- odds ratios.

Risk of development of active TB

Meta analysis of the results of a positive test associated with graded exposure to active TB was performed from six studies (Brock et al. 2004; Chun et al. 2008; Hansted et al. 2009; Higuchi et al. 2009; Lighter et al. 2009; Okada et al. 2008).

There were two longitudinal studies (Higuchi et al. 2007; Higuchi et al. 2009) that followed up participants to investigate the development of active TB.

Five studies (Anon ; Brock et al. 2004; Chun et al. 2008; Connell et al. 2006; Okada et al. 2008) looked at the concordance between IGTs and Mantoux tests.

Evidence statements

Moderate quality evidence from six studies with 935 children aged 0–18 years showed that a positive IGT was more strongly associated with increasing TB exposure than a positive Mantoux test (ratio of odds ratio 2.86 [95% CI 1.56 to 5.23]).

Low quality evidence from two studies that followed up 281 children aged 8–16 years who had a negative IGT test found that none had developed active TB within 888.5 person–years. Each child had been followed up for an average of just over 3 years. All the children had tested positive with a Mantoux test but 99% were BCG vaccinated. The studies were from the same group in Japan.

Moderate quality evidence from two studies with 110 children found that there was a low-to-moderate level of concordance between IGTs and Mantoux tests but a high level of concordance between the two commercial IGTs.

Low quality evidence from five studies with 461 children aged 0–18 years showed a wide variation in concordance between IGTs and Mantoux tests (kappa values ranging from 0.19 to 0.866). These studies were conducted in very diverse populations with different rates of BCG vaccinations and wide age ranges.

Evidence to recommendations

Because of their underdeveloped immune system, children would be more likely to develop active and more serious disease if they had latent infection. This risk is greater in children aged under 5 years.This could lead to disability or death depending on the location of the infection. The GDG observed that the evidence presented that determined the negative predictive values of the tests was of very low quality. It also felt that the generalisability of those studies could be an issue especially with regard to the BCG vaccination program in Japan. It was agreed that most paediatricians would choose to treat a high-risk child if they had a positive Mantoux test and negative IGT because there was very limited evidence to suggest that a negative IGT could completely exclude infection. The difficulty of phlebotomy and obtaining enough blood in children was discussed, generally in those under five years of age and especially when they are under two years. Indeterminate IGT results occur more frequently in younger children. The GDG was of the view that IGTs perform less well in younger children. The group also agreed that careful consideration should be given to high-risk young children, especially those aged under 5 years because false-negative results could have substantial implications.

2006, amended 2011

Table 10 Diagnosis of latent TB in children

Study	Results[1] (IGT versus Mantoux tests in children aged 0–18 years)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Meta-analysis (six studies) (Brock et al. 65–9;Chun et al. 389–94;Hansted et al. 41;Okada et al. 1179–87;Higuchi et al. 352–57;Lighter et al. 30–37)	ROR ranged from 0.70 to 10.09. The overall ROR value was 2.86 (95% CI 1.56 to 5.23). A value greater than 1 in this case means that IGT was more strongly associated with TB exposure than Mantoux test.	Y	Y	N	-	N	Low

[1] Outcomes were associations between graded exposure and positive test.

Limitation was the lack of a reference test meaning the measures of effect of sensitivity and specificity could not be determined. Inconsistency was the grading of exposure differed between studies (for example, sleeping proximity, duration of exposure, contact type). Imprecision was not measurable.

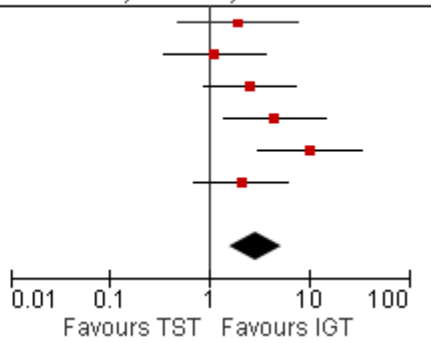
CI = confidence interval. IGT = interferon gamma test. ROR = ratio of odds ratios.

2006, amended 2011

Figure 2 Forest plot of meta-analysis of IGT and Mantoux test results based on high-risk and low-risk exposure

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Brock et al 2004(1434)	0.6576	0.7124	85	85	13.3%	1.93 [0.48, 7.80]
Chun et al 2008 (276)	0.1137	0.6096	71	71	16.3%	1.12 [0.34, 3.70]
Hansted et al 2009 (3427)	0.9398	0.5417	97	97	18.9%	2.56 [0.89, 7.40]
Higuchi et al 2009(164)	1.4986	0.6008	313	306	16.7%	4.48 [1.38, 14.53]
Lighter et al 2009 (282)	2.3114	0.6039	174	174	16.5%	10.09 [3.09, 32.95]
Okada et al 2008(393)	0.7371	0.556	195	195	18.3%	2.09 [0.70, 6.21]
Total (95% CI)			**935**	**928**	**100.0%**	**2.86 [1.56, 5.23]**

Heterogeneity: Tau² = 0.21; Chi² = 7.94, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 3.40 (P = 0.0007)



Both OR and ROR in this context, reflect test performance and provide an approach to evaluating tests in the absence of a reference test. OR is a function of test sensitivity and specificity and increases as one or both of these measures increase. Statistically OR = [sensitivity/(1-specificity)]/[(1-sensitivity)/specificity]

CI = confidence interval. IGT = interferon gamma test. OR = odds ratio. ROR = ratio of odds ratios. SE = standard error. See appendix L for definitions of high and low risk.

2006, amended 2011

Table 11Diagnosing latent TB in children (predicting development of active TB)

Study	Results[1] (IGT versus Mantoux test in children aged 8–16 years)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Two studies (Higuchi et al. 88–92;Higuchi et al. 352–7)	281 children with negative IGT but positive Mantoux test were followed up for a total of 888.5 person–years. None developed active TB. Mean duration of follow-up was 3 years. 99% of participants were BCG-vaccinated. Negative predictive value = 100%	Y	N	N	-	N	Moderate

[1] Outcome was prognostic value of IGT in predicting the subsequent development of potential active TB. Imprecision was not measurable. Limitations were defined as number of participants too few and follow-up too short for a precise result to be determined.

BCG = Bacille Calmette-Guerin. IGT = interferon gamma test; TB = tuberculosis.

2006, amended 2011

Table 12 Diagnosis of latent TB in children (agreement between tests)

Study	Results (IGT versus Mantoux test in childrenaged 0–18 years)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Five studies (Connell et al. 616–20;Connell et al. e2624;Brock et al. 65–9;Chun et al. 389–94;Okada et al. 1179–87)	Concordance between IGT and Mantoux tests as measured by kappa values ranged from 0.19 to 0.866	Y	Y	N	–	N	Low

Outcome was concordance between Mantoux test and IGT. Limitation was the lack of a reference test therefore sensitivity and specificity could not be determined. Inconsistency was that the grading of exposure differed between studies (for example, sleeping proximity, duration of exposure, contact type). Imprecision was not measurable.

IGT = interferon gamma test. TB = tuberculosis.

2006, amended 2011

5.1.6 Diagnosis of latent TB in people who have been in close contact with a person with active TB

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent TB in people who have been in close contact with a person with active TB?

Evidence review

Of the 27 papers selected:

- Mantoux test thresholds ranged from 5 mm to 30 mm
- 11 papers graded TB exposure, risk and proximal contact and it was possible to pool the results (Anon ; Alvarez-Leon et al. 2009; Brodie et al. 2008; Casas et al. 2009; Diel et al. 2008; Girardi et al. ; Kang et al. 2005; Kik et al. 2009; O'Neal et al. 2009; Topic et al. 2009; Zellweger et al. 2005)
- 16 papers (Adetifa et al. 2007; Alvarez-Leon et al. 2009; Arend et al. 2007; Brodie et al. 2008; Casas et al. 2009; Diel et al. 2009; Hesseling et al. 2009; Kang et al. 2005; Kik et al. 2009; Mirtskhulava et al. 2008; Pai et al. 2005; Porsa et al. 2007; Topic et al. 2009; Tripodi et al. 2009; Vinton et al. 2009; Zellweger et al. 2005) analysed the degree of concordance between Mantoux tests and IGT
- there were two longitudinal studies (Diel et al. 2008) which followed up participants to investigate the development of active TB.

2006, amended 2011

Table 13 Diagnosing latent TB in people who have been in close contact with a person with active TB.

Study	Results (IGT versus Mantoux test)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Meta analysis of 11 studies: Alvarez-Leon et al. (2009); Brodie et al. (2008); Casas et al. (2009); Diel et al. (2008); Girardi et al. (2009); Kang et al. (2005); Khanna et al. (2009); Kik et al. (2009); O'Neal et al. (2009); Topic et al. (2009); Zellweger et al. (2005).	Greater than 1 in this case means that positive IGT was more strongly associated with TB exposure than positive Mantoux test. The overall ROR value was 1.54 (1.08 to 2.19)	Y	Y	N	-	N	Low
Meta analysis of six studies: Brodie et al. (2008), Kang et al. (2005), Khanna et al. (2009), Kik et al. (2009), Topic et al. (2009), Zellweger et al. (2005).	The overall ROR value was 2.07 (1.23 to 3.48). Greater than 1 in this case means that positive IGT was more strongly associated with TB exposure than positive Mantoux test when BCG vaccination rate was greater than 50%.	Y	Y	N	-	N	Low
Meta analysis of five studies: Alvarez-Leon et al. (2009), Casas et al. (2009), Diel et al. (2008), Girardi et al. (2009), O'Neal et al. (2009)	The overall ROR value was 1.25 (0.94 to 1.67). Greater than 1 in this case means that positive IGT was more strongly associated with TB exposure than positive Mantoux test when BCG vaccination rate was less than 50%.	Y	Y	N	-	N	Low
Children were considered as a separate population. Outcome was diagnosis of latent TB in contacts from meta-analysis of ROR for IGT versus Mantoux test. Limitation was the lack of a reference test meant the measures of effect of sensitivity and specificity could not be determined. Inconsistency was that the grading of exposure differed between studies (for example, sleeping proximity, duration of exposure, contact type). Imprecision was not measurable. BCG = Bacille Calmette-Guerin. IGT = interferon gamma test; ROR = ratio of odds ratios. TB = tuberculosis							

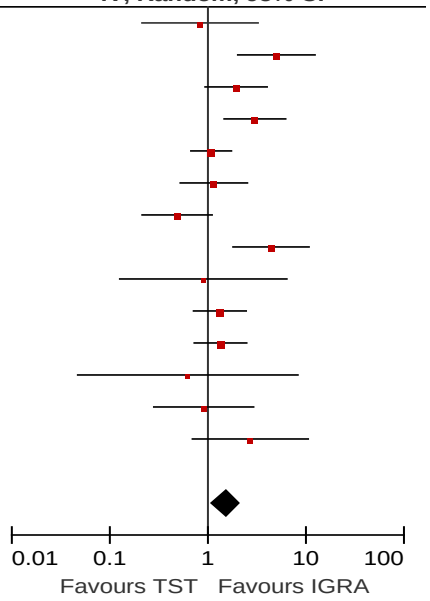
2006, amended 2011

Figure 3 Forest plot of meta-analysis of IGT and tuberculin skin test results based on high-risk and low-risk exposure to active TB

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Alvarez-Leon etal2009(23)	-0.1839	0.6933	134	134	4.6%	0.83 [0.21, 3.24]
Brodie etal 2008 (479)	1.6094	0.4612	96	96	7.4%	5.00 [2.02, 12.35]
Casas et al 2009(3428)	0.663	0.3696	143	143	9.0%	1.94 [0.94, 4.00]
Casas et al 2009(3428)	1.1048	0.3666	0	0	9.0%	3.02 [1.47, 6.19]
Diel et al 2008 (455)	0.0768	0.2414	601	601	11.5%	1.08 [0.67, 1.73]
Girardi et al 2009(3408)	0.1402	0.4001	115	115	8.4%	1.15 [0.53, 2.52]
Girardi et al 2009(3408)	-0.7222	0.417	0	0	8.1%	0.49 [0.21, 1.10]
Kang et al 2005(1199)	1.4838	0.453	120	120	7.5%	4.41 [1.81, 10.72]
Khanna etal 2009(112)	-0.1076	0.9991	147	126	2.6%	0.90 [0.13, 6.36]
Kik et al 2009(60)	0.2819	0.3135	282	282	10.0%	1.33 [0.72, 2.45]
Kik et al 2009(60)	0.2965	0.3122	0	0	10.1%	1.35 [0.73, 2.48]
O'neal et al 2009 (137)	-0.471	1.3176	61	61	1.6%	0.62 [0.05, 8.26]
Topic et al 2009 (226)	-0.0976	0.5956	54	54	5.6%	0.91 [0.28, 2.91]
Zellweger et al2005(1101)	0.9963	0.6917	91	91	4.6%	2.71 [0.70, 10.51]
Total (95% CI)			**1844**	**1823**	**100.0%**	**1.54 [1.08, 2.19]**

Heterogeneity: Tau² = 0.22; Chi² = 29.36, df = 13 (P = 0.006); I² = 56%

Test for overall effect: Z = 2.40 (P = 0.02)



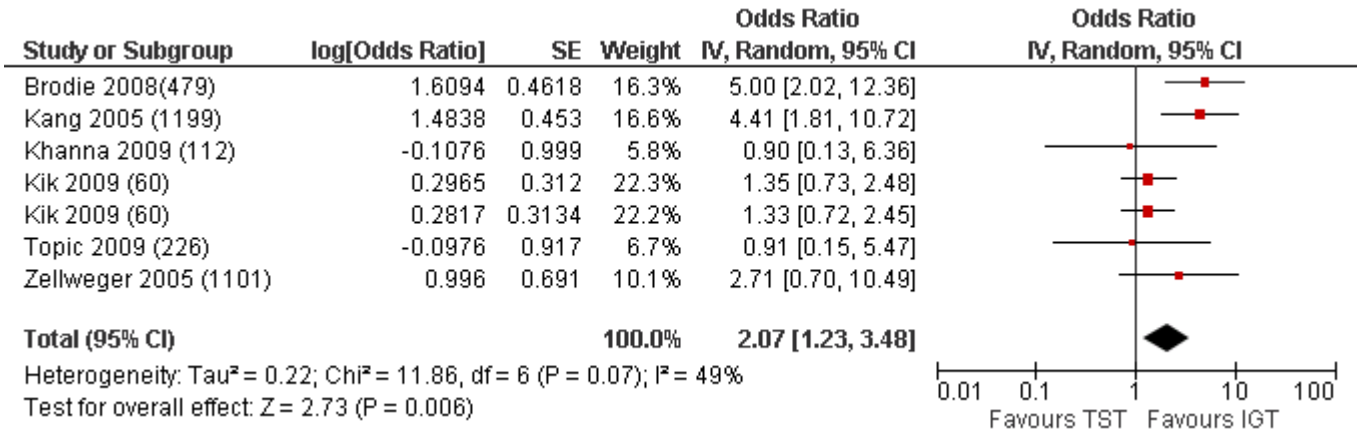
Both OR and ROR in this context, reflect test performance and provide an approach to evaluating tests in the absence of a reference test. OR is a function of test sensitivity and specificity and increases as one or both of these measures increase. Statistically OR= [sensitivity/ (1-specificity)]/ [(1-sensitivity)/specificity].

IGT = interferon gamma test. OR = odds ratio. ROR = ratio of odds ratios. TB = tuberculosis. See appendix L for definitions of high and low risk exposure.

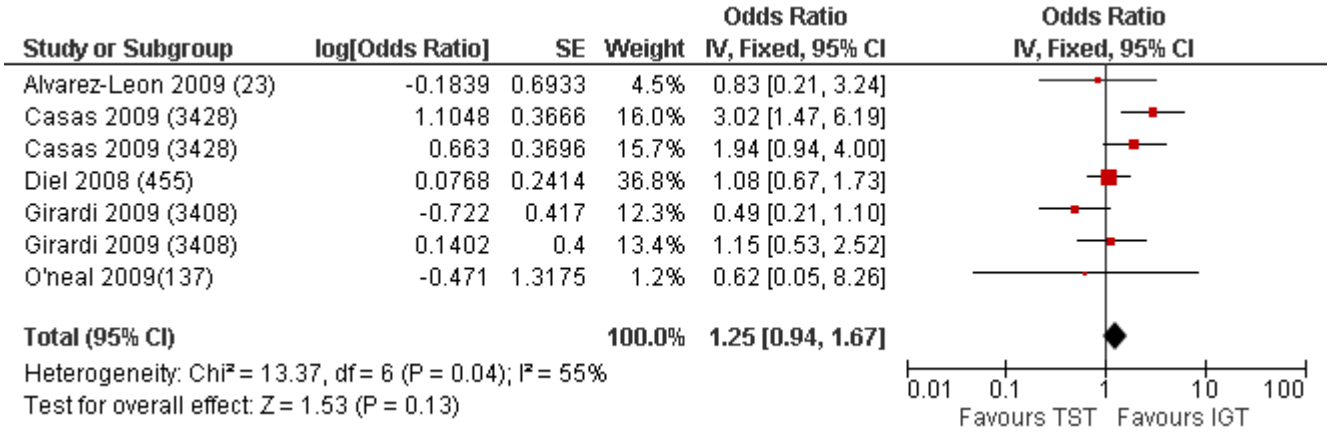
2006, amended 2011

Figure 4 Forest plot of meta-analysis of IGT and tuberculin skin test results based on high-risk and low-risk exposure to active TB stratified by BCG vaccination rates

>50% BCG-vaccinated



<50% BCG-vaccinated



2006, amended 2011

BCG = Bacille Calmette-Guerin. CI = confidence interval. IGT = interferon gamma test. IV = TB = tuberculosis. See appendix L for definitions of high and low risk exposure.

Table 14 Diagnosis of latent TB in people who have been in close contact with a person with active TB (concordance between results).

Study	Results (IGT versus Mantoux test)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Sixteen studies[1] (Kang et al. 2756–61;Mirtskhulava et al. 513–9;Tripodi et al. 30;Pai et al. 2746–55;Casas et al. e6686;Topic, Dodig, and Zoricic-Letoja 103–8;Vinton et al. 215–21;Alvarez-Leon et al. 876–83;Hesseling et al. 840–6;Adetifa et al. 122;Brodie et al. 869–74;Porsa, Cheng, and Graviss 714–9;Kik et al. 820–8;Zellweger et al. 1242–7;Arend et al. 618–27;Diel et al. 1010–8)	Overall agreement range was 46.6–94%. Kappa values were 0.11–0.85	Y	N	Y	–	N	Low

2006, amended 2011

Diel et al. (2008)[2]	None of the 25 patients who were IGT positive and started treatment had developed active TB. Six of 41 patients (14.6%) who were IGT positive but refused treatment later developed active TB. Five of 219 patients (2.3%) who were Mantoux test positive and were not treated later developed active TB. These patients were followed-up for 2 years	Y	N	N	-	N	Low
Kik et al. (2009)[2]	Positive predictive values were Mantoux test ≥ 10 mm = 3.1%; Mantoux test ≥ 15 mm = 3.8%; QFT = 2.8% ; T-SPOT = 3.3% Negative predictive values were Mantoux test ≥ 10 mm = 100%; Mantoux test ≥ 15 mm = 99.3%; QFT = 98%; T-SPOT = 98.3% These patients were followed-up for median of 1.83 years	Y	N	N	-	N	Low

Children were considered as a separate population.

[1] Outcomes were diagnosis of latent TB in contacts and degree of concordance between Mantoux test and IGT results.

[2] Outcomes were diagnosis of TB in children and the prognostic value of IGT in predicting the subsequent development of potential active TB.

Imprecision was not measurable. Limitations were too few participants and too short a follow-up

IGT = interferon gamma test. QFT = QuantiFERON-TB . TB = tuberculosis. TSPOT = T-SPOT.TB

2006, amended 2011

Evidence Statement

Low quality evidence from 11 studies with 1844 participants showed that positive IGTs were more strongly associated with increasing TB exposure than positive Mantoux tests (ROR = 1.54 [95% CI 1.08 to 2.19]). In those studies with less that 50% BCG-vaccinated patients the ratio of odds ratio was 1.25 (95% CI 0.94 to 1.67), whereas in those with over 50% BCG-vaccinated patients it was 2.07 (95% CI 1.23 to 3.48).

Low quality evidence from 16 studies showed that the degree of concordance between Mantoux test and IGT results, as measured by kappa values, was between 0.11 and 0.85.

Low quality evidence from one study showed IGTs were more likely to detect progression to active TB than Mantoux tests over a 2-year period. Positive predictive values were 14.6% and 2.3% respectively.

Low quality evidence from one study following up 339 immigrant contacts for a median of 1.83 years showed that IGTs and Mantoux tests were similar in detecting progression to active TB. Positive predictive values were 3.1% and 3.8% for Mantoux test thresholds of 10 mm and 15 mm and 2.8% and 3.3% for QFT and T-SPOT. Negative predictive values were 100%, 99.3%, 98% and 98.3% respectively.

Evidence to recommendations

The population of this group included healthcare workers who were in contact with people with active TB and non healthcare workers, who by way of residence, had been in close contact with a person with active TB. The GDG was presented with evidence showing the meta-analysis of ROR for comparing IGTs with Mantoux tests. This was stratified by percentage BCG vaccination. When adjusted for BCG vaccination, IGTs showed a better ROR than Mantoux tests. The GDG felt that although IGTs seemed better from ROR, the evidence was of poor quality and that recommendations should ideally be based on longitudinal studies that aimed to determine positive and negative predictive values of a person developing active TB.

2006, amended 2011

Evidence to recommendations – health economics (contacts)

The health economic analysis for contacts was extrapolated to this population. This analysis indicated that there was uncertainty over which testing strategy was the optimal choice. Therefore, the GDG considered that both tests should be offered and that depending on operational issues, the most appropriate should be used.

5.1.7 Diagnosis of latent TB in people who are immunocompromised

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent TB in people who are immunocompromised?

Evidence review

Of the 16 papers selected:

- five papers (Balcells et al. 2008; Jones et al. 2007; Luetkemeyer et al. 2007; Mandalakas et al. 2008; Talati et al. 2009) looked at people with HIV. The paper by Mandalakas et al. (2008) also had a children's population.
- seven papers (Bartalesi et al. 2009; Cobanoglu et al. 2007; Matulis et al. 2008; Ponce de et al. 2008; Shovman et al. 2009; Soborg et al. 2009; Vassilopoulos et al. 2008) looked at participants who had rheumatoid arthritis, or rheumatic or inflammatory disease
- one study (Richeldi et al. 2009) combined people with HIV, who have had a liver transplant and who have haematological malignancy
- one paper (Manuel et al. 2007) looked at participants with chronic liver disease
- one paper (Piana et al. 2006) investigated patients in the haematology department who were immunosuppressed
- one (Schoepfer et al. 2008) looked at people with Crohn's disease and ulcerative colitis

Table 15 Diagnosis of latent TB in patients who are immunocompromised

Study	Results (discordance between Mantoux test and IGT in 973 people with HIV)	Limitation	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Five studies (Balcells et al. 645–52;Luetkemeyer et al. 737–42;Talati et al. 15;Jones et al. 1190–5;Mandalakas et al. 417–23)	Overall discordance 0– 29.7%	Y	Y	N	–	Y	Low
	Mantoux test positive:IGT negative discordance 1.8–28.6%						
	Mantoux test negative:IGT positive discordance 0–29.7%						

Limitations: The lack of a reference test meant the crucial measures of effect of sensitivity and specificity could not be determined. Inconsistencies were noted in study designs: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design, others were diagnostic and some studies seemed to be a hybrid of both. Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was difficult because the performance of the tests depended on the immunocompetence of the participants.

IGT = interferon gamma test TB = tuberculosis.

2006, amended 2011

Table 16 Diagnosis of latent TB in children who are immunocompromised

Study	Results (discordance between Mantoux test and IGT in 23 children with HIV and mean age 4.4 years (range 1.1–11.1 years)	Limitation	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
One study Mandalakas et al. 417–23	Overall discordance 0–39.1%	Y	N	N	–	Y	Low
	Mantoux test positive:IGT negative discordance 13–25%						
	Mantoux test negative:IGT positive discordance 0– 39.1%						

Limitations were that the lack of a reference test meant the crucial measures of effect of sensitivity and specificity could not be determined: Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was difficult because the performance of the tests depends on the immunocompetence of the participants.

IGT = interferon gamma test. TB = tuberculosis.

2006, amended 2011

Table 17 Diagnosis of latent TB in people who are immunocompromised (indeterminate results)

Study	Results (indeterminate IGT results in people with HIV)	Limitation	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Three studies Luetkemeyer et al. 737–42;Talati et al. 15;Jones et al. 1190–95	1.83–17.87%	Y	Y	N	–	Y	Low
	Odds ratio for indeterminate results adjusted for CD4 count: below 100 cells /mm³ 4.8 (95% CI 1.55 to 4.75), 34.81 (95% CI 7.98 to 151.89) below 200 cells/mm³ 3.6 (95% CI 1.9 to 6.8), 47.58 (95% CI 5.89 to 384.5)	Y	Y	N	-	Y	Low

Limitations were that the lack of a reference test meant the crucial measures of effect of sensitivity and specificity could not be determined. Inconsistencies were in study design: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design, others were diagnostic and some seemed to be a hybrid of both. Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was difficult because the performance of the tests depends on the immunocompetence of the participants.

CI = confidence interval. IGT = interferon gamma test. TB = tuberculosis.

2006, amended 2011

Table 18 Diagnosis of latent TB in people with rheumatoid arthritis who are immunocompromised

Study	Results (discordance between IGT and Mantoux test in 1121 people)	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Seven studies in people with rheumatoid arthritis (Vassilopoulos et al. 1271–6;Ponce de et al. 776–81;Bartalesi et al. 586–93;Cobanoglu et al. 1177–82;Soborg et al. 1876–84; Matulis et al. 84–90;Shovman et al. 1427–32)	Overall discordance 12.2–44.3%	Y	Y	N	–	Y	Low
	Mantoux test positive:IGT negative discordance 5.9–47.5%						
	Mantoux test negative, IGT positive discordance 1.6–23.7%						

Limitations were that the lack of a reference test meant the crucial measures of effect of sensitivity and specificity could not be determined. Inconsistencies were in study design: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design, others were diagnostic and some seemed to be a hybrid of both. Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was a challenge because the performance of the tests depends on the immunocompetence of the participants.

IGT = interferon gamma test. TB = tuberculosis.

2006, amended 2011

Table 19 Diagnosis of latent TB in people who are immunocompromised (association between risk factors and positive test)

Study	Results (people with rheumatoid arthritis)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Two studies Soborg et al. 1876–84;Matulis et al. 84–90	Corticosteroid treatment: OR with IGT 1.11 (95% CI 0.30 to 4.14); RR with IGT 0.5 (95% CI 0.1 to 1.6) No Corticosteroid treatment: OR with Mantoux test 0.74 (95% CI 0.32 to 1.72); RR with Mantoux test 0.4(95% CI 0.1 to1.0)	Y	Y	N	-	Y	Low
	Disease-modifying antirheumatic drug treatment: OR with IGT 2.34 (95% CI 0.52 to 10.6); RR with IGT 0.7 (95% CI 0.3 to 1.7) No disease-modifying antirheumatic drug treatment: OR with Mantoux test 0.75 (95% CI 0.32 to 1.77); RR with Mantoux test 1.3 (95% CI 0.7 to 2.3) RR Mantoux test = 1.5 (95% CI 0.7 to 2.9)						

Limitations were that the lack of a reference test meant the crucial measures of effect of sensitivity and specificity could not be determined. Inconsistencies were in study design: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design, others were diagnostic and some seemed to be a hybrid of both. Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was a challenge because the performance of the tests depends on the immunocompetence of the participants.

CI = confidence interval. IGT = interferon gamma test. OR = odds ratio. RR = relative risk. TB = tuberculosis

2006, amended 2011

Table 20 Diagnosis of latent TB in people with haematological conditions who are immunocompromised

No of studies	Results (discordance between IGT and Mantoux test in 380 people with haematological conditions)	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
3 studies (Piana et al. 31–4;Manuel et al. 2797–801; Richeldi 2009 et al. 198–204)	Overall discordance 9–32.2%	Y	Y	N	–	Y	Low
	Mantoux test positive:IGT negative discordance 2.6–8.5%						
	Mantoux test negative:IGT positive discordance 6.4–29.6%						
Limitations were that the lack of a reference test meant the measures of effect of sensitivity and specificity could not be determined. Inconsistencies were in study design: although all studies were observational, some were cross-sectional, and others were retrospective. Some studies were prognostic in design and others were diagnostic and some seemed to be a hybrid of both. Imprecision was not measurable. Other considerations were that measuring the diagnostic value of the tests in this population was a challenge since the performance of the tests depends on the immunocompetence of the participants. IGT = interferon gamma test. TB = tuberculosis.							

2006, amended 2011

Evidence Statement

Low quality evidence from five studies showed that the level of discordance between IGTs and Mantoux tests in 973 adults with HIV ranged from 0% to 29.7% for negative Mantoux tests/positive IGTs and 1.8% to 28.6% for positive Mantoux tests/negative IGTs.

Low quality evidence from one study showed that in 23 children with HIV (mean age of 4 years) the positive Mantoux tests/negative IGTs discordance ranged from 13% to 25% and negative Mantoux tests/positive IGTs discordance ranged from 0 to 39.1% similar overall discordance

Low quality evidence from three studies showed that the rate of indeterminate results from an IGT test in 837 people with HIV ranged from 1.83% to 17.87%. The rate of indeterminate results was significantly higher in those with a CD4 count below 200cells/mm^3.

Low quality evidence from seven studies showed that in 1121 individuals with rheumatoid arthritis, the overall discordance between IGTs and Mantoux tests was between 5.9% and 47.5% for positive Mantoux tests/negative IGTs, and 1.6% to 23.7% for negative Mantoux tests/positive IGTs.

Low quality evidence from two studies showed that the level of discordance in patients with diseases including, chronic liver disease, non-Hodgkin's lymphoma, multiple myeloma, acute myeloid leukaemia, and chronic myeloma was between 6.4% and 29.6% for negative Mantoux tests/positive IGTs, and 2.6% and 8.5% for positive Mantoux tests/negative IGTs.

Evidence to recommendations

The GDG pointed out that it was important to differentiate the groups of people who were immunocompromised. The group agreed that the degree and type of immunosuppression was also important. There was general agreement that the evidence was of low quality. There was a lot of discordance between the tests in the immunocompromised population, but in general IGTs may identify more truly positive latent TB infections than Mantoux tests but the value of such tests varies with the nature and the degree of immunosuppression. The group discussed the stratification of some

of the HIV studies by CD4 count and agreed on the basis of the evidence presented that a CD4 count below 200cells/mm^3 was significantly associated with an indeterminate result. The group also strongly felt that people with HIV who have a CD4 count of 500cells/mm^3 or more should be tested in the same way as people who are immunocompetent because the tests would perform in a similar way in these two groups of people. Evidence that looked at the effect specific anti-TNFalpha medications had on the diagnosis of latent TB was not identified.

Evidence to recommendations – Health economics (immunosuppresion)

No health economic modelling was conducted in this patient group. However the modelling for contacts and people from high prevalence countries indicated that high rates of transformation from latent TB to active TB and worse outcomes would all result in improved cost-effectiveness estimates for the testing strategies.

5.1.8 Screening for latent TB in healthcare workers

Key clinical question

What is the effectiveness of screening using IGT for healthcare workers?

Evidence review

Although studies that included healthcare workers had been analysed as part of the contact tracing question (section 5.1.6), the GDG advised that screening in healthcare workers should be specifically looked at. This was because the GDG felt that the scope was open to interpretation with regard to pre-employment screening in the NHS. It was difficult to identify studies that were screening for latent TB in healthcare workers. Good quality studies would have been those which compared participants who had been screened for latent TB and offered treatment as appropriate with those who had not and followed up to determine those who developed active TB. No such studies were identified.

Five studies were selected for critical appraisal. Of these:

- two (Alvarez-Leon et al. 2009; Harada et al. 2006) looked at existing employees

- two (Cummings et al. 2009; Hotta et al. 2007) looked at newly hired workers
- two (Harada et al. 2006; Hotta et al. 2007) had participants of whom most were BCG vaccinated
- three (Alvarez-Leon et al. 2009; Hotta et al. 2007; Zhao et al. 2009) determined concordance and discordance.

The evidence from these screening studies was of very low quality. Most of the issues had already been addressed and analysed in the contact tracing question. Table 21 summarises this evidence.

Table 21 Effectiveness of IGTs for screening healthcare workers

Study	BCG vaccination	Healthcare workers	Discordance Positive Mantoux test/negative IGT	Discordance Negative Mantoux test/positive IGT
Cummings et al.	93% did not report BCG vaccination	Newly hired	Not determined	Not determined
Harada et al.	95%	Existing employees	Not determined	Not determined
Zhao et al.	Not indicated	Not indicated	25%	0%
Hotta et al.	Most BCG vaccinated	Newly hired	56.5%	0%
Alvarez-Leon et al.	35.1%	Existing employees	4%	2%

BCG = Bacille Calmette-Guerin. IGT = interferon gamma test.

Evidence statements

Evidence from three low quality papers showed that there was more discordance between positive Mantoux tests/negative IGT results than negative Mantoux tests/positive IGT results in 381 healthcare workers. Negative Mantoux tests/positive IGTs discordance was very low (less than 2%). Some of the healthcare workers were newly employed. Coverage and timing of BCG vaccination was variable. In two other studies discordance figures were not quantified.

Evidence to Recommendations

The GDG agreed that the level of evidence for screening studies was low. It also considered that healthcare workers would fall into the category of people

from high prevalence countries or individuals who had had contact with a person with active TB. They made recommendations based on the evidence from those populations. For healthcare workers who were immunocompromised, the recommendations for the immunocompromised group applied.

Health economics – Contact tracing for healthcare workers (this section also relates to the diagnosis of latent TB in people who have been in close contact with a person with active TB)

The economic model used the same structure, costs and health-related quality of life values as those in the model for adults from high prevalence countries. However, the difference is in the estimates of the test accuracy and the prevalence of latent TB infection in this cohort. The test accuracy was based on Girardi et al. (2009) and Diel et al. (2010). The baseline prevalence used was 20%.

The model assumed the treatment regimen was the same as for people from high prevalence countries and that diagnosing and screening for latent TB was done in an outpatient setting.

The base case analysis for this population is shown in table 22.

2006, amended 2011

Table 22 Cost-effectiveness of testing strategies for contacts

Strategy	Cost (£)	Effect (QALY loss)	ICER compared with no test (£)	Net monetary benefit (£20,000 per QALY gained)
Girardi et al. (2009)				
No test	380	9.9393	-	-
Mantoux test/IGT	476	9.9473	12,037	£64
IGT	531	9.9483	16,833	£29
Mantoux test	604	9.9484	24,637	-£42
Diel et al. (2010)				
No test	380	9.9393	-	-
Mantoux test/IGT	445	9.9435	15,174	£21
IGT	515	9.9473	16,244	£25
Mantoux test	567	9.9447	Dominated	Dominated

ICER = incremental cost-effectiveness ratio. IGT = interferon gamma test. QALY = quality-adjusted life year.

These results indicate that Mantoux test/IGT and IGT alone are both cost-effective testing options and that depending on the test accuracies used either option could be the optimum choice.

Table 23 presents sensitivity analysis on the prevalence of latent TB in this conctacts population. The transformation rate did not appear to be a major variable in the model. Results are reported as net monetary benefits at the £20,000 per QALY gained threshold.

2006, amended 2011

Table 23 Net monetary benefits at £20,000 per QALY gained for different prevalence rates and test accuracy sources for contact tracing

Prevalence	Mantoux test/IGT	IGT	Mantoux test
Girardi et al. (2009)			
0.01	−36	−97	Dominated
0.05	−15	−71	Dominated
0.1	11	−37	Dominated
0.15	38	−4	−83
0.2	64	29	−42
0.25	90	62	−1
0.3	116	95	40
Diel et al. (2010)			
0.01	−31	−85	Dominated
0.05	−20	−61	Dominated
0.1	−7	−33	Dominated
0.15	7	−3	Dominated
0.2	21	25	Dominated
0.25	34	54	Dominated
0.3	48	83	Dominated

At £20,000 per QALY gained the prevalence has to be over 10% for testing to be cost effective. At a £30,000 per QALY gained threshold the lowest prevalence rate that testing remains cost effective at is 6%. In the contacts model, the transformation from latent to active TB was implemented by a relative risk (please see 2006 guideline appendix L for more details) the net monetary results at £20,000 per QALY gained are presented in table 24.

2006, amended 2011

Table 24 Net monetary benefits at £20,000 per QALYgained for different transformation rates and test accuracy sources for contact tracing

Latent TB to active TB	Mantoux test/IGT	IGT	Mantoux test
Girardi et al. (2009)			
0	18	−23	−96
1	29	−10	−82
2	41	3	−69
3	52	16	−56
4	64	29	−42
5	75	42	−29
6	87	55	−16
Diel et al. (2010)			
0	−3	−20	Dominated
1	3	−9	Dominated
2	9	2	Dominated
3	15	14	Dominated
4	21	25	Dominated
5	27	36	Dominated
6	32	48	Dominated

These results indicate that if the risk of latent TB becoming active is high then the cost-effectiveness results improve for all the options.

These results also indicate that IGT or Mantoux test/IGT could be the optimum choice but that it is highly dependent on the prevalence of latent TB in the population.

Evidence to recommendations – health economics (healthcare workers and screening)

Testing for healthcare workers who have come into contact with someone with active TB should follow the recommendations for all people who have been in contact with a person with active TB.

No specific health economic modelling was conducted for this population group. However, evidence from the high prevalence country and contacts analysis indicates that the testing strategies may be cost effective because the outcomes of a healthcare worker contracting TB might be more significant than a regular adult contact. Therefore, given the uncertainties in the model and difference in local circumstances both tests should be offered.

Summary evidence to recommendations

IGTs showed little evidence of being affected by prior BCG vaccination, and showed stronger correlation with exposure categories than the Mantoux tests. This was shown in high prevalence groups and in those who have been in contact with a person with active TB. The specificity of IGTs seemed better, and there was less potential for false-positive results. It was not possible to determine, for either Mantoux tests or IGTs, the rate of false-negative results. The GDG felt that some people with false-negative results would develop active TB and therefore reduce the cost effectiveness of vaccination and treatment of latent TB infection.

High quality prospective studies in people with latent TB (as diagnosed by positive IGTs) found at TB contact tracing and new entrant screening, have not yet been performed to find what proportion of such persons went on to develop clinical disease.

Economic modelling was undertaken with various strategies from no action to a two-step strategy with either Mantoux tests followed by interferon-gamma testing, or serial IGTs. Of these options, the model provided most support, on grounds of cost-effectiveness, for a two-step approach with an initial Mantoux test, followed by an interferon-gamma test to confirm positivity. The GDG members also supported this because of clinical utility and feasibility.

In the studies evaluated, IGT show a stronger correlation with exposure than Mantoux tests. Much of the discordance between a positive Mantoux test and a negative IGT can be accounted for by prior BCG vaccination. The GDG agreed that in the absence of good quality longitudinal studies the relative benefit of IGT over Mantoux test in determining the need for treatment of latent infection is not certain. However they made recommendations in populations where they considered IGT to be of clear benefit especially in cases where IGT would reduce the uncertain diagnosis of Mantoux tests.

No further evidence was reviewed for other groups such as Prisoners/prison staff and nursing homes. However, the GDG felt that the tests should perform as with any other adults.

5.1.9 Evidence statements

Test results and TB exposure

In a UK study{17} of healthy adults in a contact tracing clinic, IGT (ESAT-6 ELISPOT assay) results had a strong positive relationship with increasing intensity of contact exposure (OR 9.0 per unit increase in exposure, 95%CI 2.6 to 31.6, p=0.001), whereas Mantoux test results had a weaker relationship with exposure (OR 1.9, 95%CI 1.0 to 3.5, p=0.05). (**2**)

In a study{11} of students aged 11–15 years in the UK from the same school as an index case, the odds of a test result being positive for each increase across four stratified exposure groups increased by a factor of 2.78 (95%CI 2.22 to 3.48, p<0.0001) for the IGT (ESAT-6/CFP10 ELISPOT assay) and 2.33 (95%CI 1.88 to 2.88, p<0.0001) for the Mantoux test. The IGT correlated significantly better with increasing exposure across the four groups than the Mantoux test (p=0.03). The odds of a positive IGT result increased by a factor of 2.51 (95%CI 1.58 to 3.99, p<0.0001) with each week of direct exposure, which was significantly higher (p=0.007) than that for the Mantoux test (OR 1.30, 95%CI 1.10 to 1.54, p=0.002). (**2**)

In contacts of index cases in the Gambia,{13} with increasing *M. tuberculosis* exposure, the percentage of participants who were tuberculin positive and interferon gamma test (ESAT-6/CFP-10 ELISPOT assay) negative increased from 11% of those sleeping in a different house from the index case to 32% of those sleeping in the same room (p<0.001). (**3**)

In contacts of an index case on an Italian maternity unit,{19} the odds for a test result being positive for each increase across four stratified exposure groups (from no discernible contact to household contacts) increased by 1.93 (95%CI 1.11 to 3.35, p=0.020) for the IGT (ESAT-6/CFP-10 ELISPOT assay) but there was no significant correlation for the Mantoux test. (**3**)

In Korea where BCG vaccination is mandatory,{15} a study found that the odds of a positive test result per unit increase in exposure across four groups, increased by a factor of 5.31 (95%CI 3.62 to 7.79) for the IGT (QuantiFERON-TB Gold) and by a factor of 1.52 (95%CI 1.2 to 1.91) for the Mantoux test (p<0.001). (**2**)

2006

Test results and BCG status

Healthy adults in a contact tracing clinic in the UK,{17} had IGT (ESAT-6 ELISPOT assay) results which were not correlated with BCG vaccination status whereas Mantoux test results were significantly more likely to be positive in BCG vaccinated contacts (OR 12.1, 95%CI 1.3 to 115.7, p=0.03). (**2**)

Students aged 11–15 years from the same school as an index case in the UK{11} had IGT (ESAT-6/CFP-10 ELISPOT assays) which showed no significant relation with BCG vaccination status, however, BCG vaccinated children were significantly more likely to have higher Heaf grades than unvaccinated children (p=0.002). (**2**)

In a UK study{16} of healthy household contacts and healthy unexposed controls, ESAT-6 peptide-specific interferon-gamma-secreting cells were detected in 85% of the healthy household contacts who were tuberculin positive. None of the healthy control subjects without a history of TB exposure, responded to this IGT even though all unexposed control subjects were BCG vaccinated. (**3**)

Mantoux test negative Australian born medical students (or those born in another low TB prevalence country),{14} with no prior BCG, and no known exposure to TB, were BCG vaccinated and then tested again at five months. ESAT-6 stimulated interferon-gamma levels (using ESAT-6 QuantiFERON) were very low or undetectable in all students both before and after BCG vaccination. Of these students, 46% had Mantoux test responses of 0 to 4 mm and 54% had responses of ≥5 mm. Thirteen percent had Mantoux test results of ≥10mm. Under current Australian guidelines, one student with a 16mm result was defined as having a Mantoux tes result suggestive of *M. tuberculosis* infection. (**3**)

High school contacts in a TB outbreak in Denmark{9} who had high exposure to an index case and were not BCG vaccinated, had agreement between Mantoux test and IGT (QuantiFERON-TB Gold) results of 93% (95%CI 86 to 100%). This was 95% (95%CI 88 to 102%) in the low exposure group and an overall agreement between the two tests of 94% (95%CI 89 to 99%) in all subjects tested. The kappa value was 0.866, indicating high agreement between the two tests. (**3**)

In an Italian study{19} of contacts of an index case on a maternity unit, IGT (ESAT-6/CFP-10 ELISPOT assay) results were independent of BCG vaccination status. (**3**)

IGTs were prescribed by hospital physicians for inpatients or outpatients in an Italian study with no influence from the study investigators.{12} After excluding indeterminate results, the agreement between IGT (QuantiFERON-TB Gold) and Mantoux test results was significantly lower among BCG-vaccinated individuals than in non-vaccinated individuals (41.5% *vs*. 80.3%, p<0.0001). (**3**)

In a study of healthcare workers conducted in India{18} (where non-tuberculous mycobacteria are highly prevalent), previous BCG vaccination was not associated with Mantoux test or IGT (QuantiFERON-TB Gold) positivity. (**3**)

Indeterminate test results

An Italian study{12} found that indeterminate IGT results (QuantiFERON-TB Gold) were significantly over-represented in patients with a negative Mantoux test (28.6% *vs*. 6.6% in tuberculin positive patients, p<0.001) and were more frequent in patients receiving immunosuppressive therapies than in those who were not receiving such treatments (OR 3.35, 95%CI 1.84 to 6.08, p<0.0001). Immunosuppressive therapy was defined as cancer chemotherapy, systemic steroids, or anti-tumour necrosis factor alfa agents at the time of testing. (**3**)

5.1.10 Health economics 2006

A decision model was used to compare the expected cost-effectiveness of four strategies of testing for latent infection in the context of a contact tracing programme in England and Wales. The strategies compared were:

- Mantoux test /IGT
- Mantoux test followed by IGT for patients with a positive Mantoux test
- no test (inform and advise only).

It was assumed that treatment followed current policy: with appropriate therapy for people diagnosed with active TB or testing positive for latent infection, and BCG when appropriate for others. The analysis did not compare different types of skin tests or different types of IGT.

The model is a decision tree, which does not account for the dynamics of disease transmission within the population. Instead, for simplicity, it was assumed that each primary case of active disease is associated with a fixed number of secondary

2006

cases. This is probably a reasonable assumption when comparing tests with similar sensitivity, since the absolute difference in false negatives, and hence in opportunities for transmission within the community, will be small. However, estimates of the relative cost effectiveness of contact tracing *per se* are less robust and should be treated with caution.

Various assumptions were made about the epidemiology and likely concordance with testing and treatment programmes. However, it should be noted that these factors will vary with the context of contact tracing. There is also considerable uncertainty over the relative accuracy of the Mantoux test and IGT, as well as over some of the other model parameters. Whenever possible input parameters and assumptions were based on empirical evidence, but some key parameters were estimated by the health economist and GDG.

Cost-effectiveness of testing strategies in contact tracing

The basecase economic analysis suggests that the two-stage strategy (Mantoux test /IGT) is within the range usually considered 'cost-effective', at around £26,000 per quality-adjusted life-year (QALY) gained. Compared with this, IGT is not cost-effective (over £150,000 per QALY gained). Mantoux test is both less effective and more expensive than all of the other options (it is 'dominated').

Variation in optimal strategy with context of contact tracing

The results of the economic analysis were highly dependent on the context of the contact tracing scheme – with a higher-risk cohort of contacts, the expected benefits of early diagnosis of active cases, treatment of latent infection, and vaccination will be greater. Below a prevalence of about 10% none of the testing strategies is cost-effective. At intermediate levels of prevalence (between about 10% and 40%), the two-stage Mantoux test /IGT strategy is cost effective. Above 40% IGT on its own is the most cost-effective option.

Table 25: Cost-effectiveness of diagnostic strategies

Prevalence of infection	Strategy	Cost (£)	Effect (QALYs lost)	ICER[7] (£ per QALY gained)
0	No test	£31	0.00409	–
	Mantoux test/IGT	£58	0.00394	£178,835

[7] ICER = incremental cost-effectiveness ratio

	IGT	£102	0.00394	(Dominated)
	Mantoux test	£139	0.00404	(Dominated)
10%	No test	£191	0.02533	–
	Mantoux test/IGT	£240	0.02323	£23,351
	IGT	£282	0.02290	£126,813
	Mantoux test	£314	0.02310	(Dominated)
20%	No test	£351	0.04658	–
	Mantoux test/IGT	£423	0.04252	£17,575
	IGT	£463	0.04185	£60,073
	Mantoux test	£489	0.04217	(Dominated)
30%	No test	£512	0.06782	–
	Mantoux test/IGT	£605	0.06182	£15,553
	IGT	£643	0.06081	£38,081
	Mantoux test	£664	0.06123	(Dominated)
40%	No test	£672	0.08907	–
	Mantoux test/IGT	£788	0.08111	£14,522
	IGT	£824	0.07976	£27,132
	Mantoux test	£838	0.08029	(Dominated)
50%	No test	£832	0.11031	–
	Mantoux test/IGT	£970	0.10040	£13,898
	IGT	£1,005	0.09872	£20,578
	Mantoux test	£1,013	0.09936	(Dominated)

Uncertainty over optimal testing strategy for contact tracing

The results of the economic analysis were subject to a high degree of uncertainty. The results were very sensitive to assumptions about the relative accuracy of the two types of test, the risk of current and future TB in the cohort, the level of transmission to the wider population, and also to the expected net benefit of avoiding each active case of TB.

5.1.11 From evidence to recommendations

IGTs showed little evidence of being affected by prior BCG vaccination, and showed stronger correlation with exposure categories than did Mantoux test. This was shown in low prevalence groups, in household contacts, and in outbreak situations. The specificity of IGTs seemed better, and there was less potential for false positive results. It is not possible to determine, for either a Mantoux test or IGT, the rate of false negative results. Some people with false negative results will go on to develop active TB and thus reduce the cost-effectiveness of vaccination and treatment of latent TB infection.

Prospective studies in people with latent TB (as judged by positive IGTs) found at TB contact tracing and new entrant screening, have not yet been performed to find what proportion of such persons went on to develop clinical disease.

Economic modelling was undertaken with various strategies from no action to a two-step strategy with either a Mantoux test followed by interferon-gamma testing, or serial IGTs. Of these options, the model provided most support, on grounds of cost-effectiveness, for a two-step approach with an initial Mantoux test, followed by an IGT to confirm positivity. The GDG members also supported this because of clinical utility and feasibility.

2006

RECOMMENDATIONS – Partial update 2011

These recommendations update and replace recommendation R1 from CG33.

Diagnosing latent TB

R1 Offer Mantoux testing in line with the Green Book[8] to diagnose latent TB in people who are:

- household contacts (aged 5 years and older) of all people with active TB
- non-household contacts (other close contacts for example, in workplaces and schools).

R2 Consider interferon-gamma testing for people whose Mantoux testing shows positive results, or in people for whom Mantoux testing may be less reliable, for example BCG vaccinated people.

R3 If Mantoux testing is inconclusive, refer the person to a TB specialist.

New entrants from high-incidence countries

R4 Offer a Mantoux test to children aged 5–15 years. If positive, follow with an interferon-gamma test**.**

New 2011

[8] In this guideline the 'Green Book' is the 2006 edition of 'Immunisation against infectious disease', published by the Department of Health(available from http://www.dh.gov.uk) The Green Book contains details of people who may have suppressed responses to tuberculin skin testing.

R5 Offer either an interferon-gamma test alone or a dual strategy in people aged 16–35 years. For people over 35 years, consider the individual risks and benefits of likely subsequent treatment, before offering testing. (Refer to other sections for other groups e.g. immunocompromised)

R6 Offer Mantoux testing as the initial diagnostic test for latent TB infection in children younger than 5 years who have recently arrived from a high-incidence country. If the initial test is positive (taking into account the BCG history):

- refer to a TB specialist to exclude active disease **and**
- consider treating latent TB.

Household contacts 2- 5 years

For children younger than 2 years see R83-85

R7 Offer Mantoux testing as the initial diagnostic test for latent TB infection in child household contacts between the ages of 2 and 5 years. If the initial test is positive taking into account the BCG history:

- refer to a TB specialist to exclude active disease **and**
- consider treating latent TB**.**

R8 If the initial Mantoux test is negative but the child is a contact of sputum-smear-positive disease, offer an interferon-gamma test after 6 weeks and repeat the Mantoux test to increase the sensitivity (to reduce false negative results).

Contacts – outbreak situation

R9 In an outbreak situation when large numbers of individuals may need to be screened, consider a single interferon-gamma test for people aged 5 years and older.

People who are immunocompromised

R10 If latent TB is suspected in children who are immunocompromised, refer to a TB specialist.

R11 For people with HIV and CD4 counts less than 200 cells/mm^3, offer an interferon-gamma test and a concurrent Mantoux test. If either test is positive:

- perform a clinical assessment to exclude active TB **and**
- consider treating latent TB infection.

New 2011

R12 For people with HIV and CD4 counts of 200–500 cells/mm^3, offer an interferon-gamma test alone or an interferon-gamma test with a concurrent Mantoux test. If either test is positive:

- perform a clinical assessment to exclude active TB and
- consider treating latent TB infection.

R13 For other people who are immunocompromised, offer an interferon-gamma test alone or an interferon-gamma test with a concurrent Mantoux test. If either test is positive:

- perform a clinical assessment to exclude active TB **and**
- consider treating latent TB.

Healthcare workers

R14 Offer a Mantoux test to new NHS employees who will be in contact with patients or clinical materials if the employees:

- are not new entrants from high-incidence countries **and**
- have not had BCG vaccination (for example, they are without scar, other documentation or reliable history)[9].

R15 If the Mantoux test is negative, refer to the Green Book for BCG immunisation guidance. If the Mantoux test is positive, offer an interferon-gamma test.

R16 Offer an interferon-gamma test to new NHS employees who have recently arrived from high-incidence countries or who have had contact with patients in settings where TB is highly prevalent.

R17 Healthcare workers who are immunocompromised should be screened in the same way as other people who are immunocompromised.

Hard to reach groups

R18 Offer people from hard to reach groups a single interferon-gamma test.

New 2011

[9] If there is reliable evidence of BCG vaccination, refer to the Green Book.

5.2 Diagnosing active tuberculosis

5.2.1 Clinical introduction

Signs and symptoms of respiratory TB

Primary respiratory tuberculosis is often asymptomatic, but the fact that infection has occurred is shown by the development of a positive tuberculin skin test or interferon-gamma blood test. A history of recent contact with a person with TB is the most important factor in making the diagnosis. Occasionally, tuberculin conversion is accompanied by erythema nodosum or phlyctenular conjunctivitis. Mediastinal nodal enlargement as part of the primary complex can sometimes press on or discharge into a bronchus causing collapse of the distal lung or bronchial narrowing leading to wheeze or obstruction with distal over-inflation.{22}

In children with primary TB, weight loss, or weight loss and cough, are symptoms associated with culture confirmed TB. However, about half of all children with primary TB will have no symptoms.

Post-primary tuberculosis may be asymptomatic in the early stages, but symptoms, which can be either constitutional or respiratory, soon develop. Malaise, weight loss, fever and night sweats are the common constitutional symptoms. Cough is the commonest respiratory symptom, which is initially dry and non-productive but may later become productive, with haemoptysis in a small minority of cases. Breathlessness is a late feature, usually only occurring when a substantial amount of lung is destroyed or there is a significant pleural effusion. Chest pain is relatively uncommon, but can be pleuritic if peripheral lesions are present, or of dull ill-localised nature.

A study in Sudan, grading sputum smear positivity with clinical features showed multiple chest symptoms were positively correlated with sputum smear positivity. Also, the longer the duration of symptoms, the more this correlated with sputum smear positivity.{23} A comparison of the 'classic' symptoms of tuberculosis in patients with and without tuberculosis{24} is summarised in Table 26.

Table 26: Classic symptoms of tuberculosis

Symptom	TB (n=47)	Non-TB (n=516)	Odds ratio (95% CI)
Cough	81%	77%	1.27 (0.58–2.69)

Fever	70	59	1.64 (0.85–3.15)
Weight loss	64	27	4.74 (2.53–8.86)[10]
Night sweats	55	27	3.29 (1/79–6.04)[10]
Dyspnoea	47	50	0.88 (0.48–1.60)
Chest pain	27	26	1.08 (0.55–2.11)

A multivariate analysis{25} showed that the following features were positively associated with culture proven tuberculosis:

- the presence of TB risk factors or symptoms (OR 7.9)
- a positive skin test for tuberculosis (OR 13.2)
- a high temperature (OR 2.8)
- upper lobe disease on a chest radiograph (OR 14.6)

and that the following were negatively correlated with tuberculosis:

- shortness of breath (OR 0.2)
- crackles on physical examination of chest (OR 0.29).

Signs and symptoms of non-respiratory TB

Tuberculosis can affect nearly every non-respiratory site, sometimes with a combination of respiratory and non-respiratory sites, or single or multiple non-respiratory sites.{22} As with respiratory tuberculosis, there can be systemic and site-specific symptoms. Weight loss is particularly associated with disseminated (including miliary) and gastrointestinal tuberculosis. Fever and night sweats are common in some non-respiratory sites of disease (disseminated, including miliary, and gastrointestinal TB), but are not common in others (peripheral lymph nodes, skin, bone and joint, genitourinary TB). Tuberculosis has to be considered in the differential diagnosis of an unexplained fever, particularly in those born abroad and/or in ethnic minority groups.

Because of the multiplicity of potential sites of non-respiratory TB, suggestive symptoms are considered site by site.

Signs and symptoms of lymph node TB

Nearly half of all non-respiratory TB in England and Wales occurs in peripheral lymph nodes, mainly cervical.{26},{27} The nodal enlargement in TB is usually

[10] significant difference

gradual and painless, but can be painful if rapid. The usual absence of erythema and warmth makes the classical 'cold abscess'. The nodes originally are discrete and firm, but may later mat together and become fluctuant as necrosis develops, which can discharge through the skin with sinus formation and superficial ulceration. Persistent lymphadenopathy of over four weeks duration in people other than white UK-born should be regarded as TB until proven otherwise and investigated appropriately.

Signs and symptoms of bone and joint TB

Bone and joint TB accounts for some 10–15% of non-respiratory disease, with approximately 50% in the spine, and 50% in a wide range of other bones and joints.{28},{29}

With spinal disease pain is the commonest symptom, and may be accompanied by local tenderness or slight kyphosis. Grosser kyphosis occurs when disease has progressed. Paraspinal abscesses can develop and may present as a loin mass, or as a psoas abscess pointing below the groin or causing psoas spasm with hip flexion. Compression on spinal nerve roots can mimic abdominal pathology. Extradural abscess or spinal collapse and subluxation can lead to sensory and motor symptoms involving the legs and sphincters due to spinal cord compression. Back pain and/or neurological signs should have an infective process in the differential diagnosis, particularly in ethnic minority groups.

A wide range of other joints can be involved. TB should be included in the differential diagnosis of unusual bone and joint lesions, particularly of an isolated lesion or a mono-arthritis in an ethnic minority group.

Signs and symptoms of gastrointestinal TB

This form of disease, as with nearly all other non-respiratory sites, is much commoner in ethnic minority groups. The gastrointestinal tract can be involved anywhere along its length, but peri-anal and upper gastrointestinal sites are uncommon (3% of gastrointestinal TB).{30} Series in both the developing{31} and developed world{32} show approximately one third of cases present acutely simulating abdominal emergencies and two thirds with a more gradual onset. Of the cases with an acute onset, approximately one half have right iliac fossa pain simulating acute appendicitis and the other half acute intestinal obstruction. Of

those with a more gradual onset of symptoms, fever and malaise, abdominal pain and weight loss are the commonest described symptoms,{32} being found in 72%, 60% and 58% of cases respectively in another series.{33} Abdominal distension, usually due to ascites, is reported in between 10%{32} and 65%{34} of cases. There may be right iliac fossa tenderness simulating appendicitis, or a right iliac fossa mass simulating appendix abscess or carcinoma. The ileocaecal area is the commonest site of disease. With bowel involvement there may be acute or sub-acute small bowel obstruction with vomiting and abdominal distension; there may also be palpable mass. The colon distal to the caecum is involved in up to 10% of cases{32} and is a cause of gastrointestinal bleeding.{35}

Signs and symptoms of genitourinary TB

Genitourinary TB is one of the commoner sites of non-respiratory TB in white UK-born people. For example, in 1993 it accounted for 17% of non-respiratory cases in the white UK-born ethnic group, compared with 4% in people of Indian (subcontinent) origin.{27} In white cases renal tract lesions predominate but female genital disease predominates in the Indian sub-continent ethnic group.{36}

Renal tuberculosis is often a 'silent' disease with insidious progression which can lead to total unilateral renal destruction. Systemic features such as weight loss, fever and night sweats are not common. As disease progresses, dysuria, haematuria, nocturia and pain either in the loin or anteriorly may occur. Renal disease can lead to ureteric and then bladder involvement by tubercle bacilli seeding distally. Bladder involvement initially leads to cystitis symptoms with frequency and dysuria, but as bladder wall inflammation with associated fibrosis worsens, bladder capacity falls and can be greatly reduced, the so-called 'thimble bladder' leading to marked frequency and nocturia due to a tiny bladder capacity. The urine with renal and ureteric disease, but particularly with bladder disease, shows proteinuria and haematuria on dipstick testing, and pus cells on microscopy but is sterile on standard culture. The finding of sterile pyuria should lead to the routine sending of three early morning urines for TB culture. A cold perinephric abscess can occur pointing in either the loin or like a psoas abscess in the groin. Prostatic, epididymal and testicular TB are less common. Testicular TB can present as a mass simulating testicular tumour.

Female genital TB is due to either haematogenous spread or direct spread from intra-abdominal disease. As with urological TB, systemic symptoms are uncommon unless there is associated abdominal tuberculosis. Infertility, either primary or secondary, is the commonest presentation of tubal and endometrial TB.{37} Most have no associated symptoms, but menorrhagia is reported in 20–25%, with much lower proportions having amenorrhoea or post menopausal bleeding.{37}

Signs and symptoms of disseminated (including miliary) TB

Disseminated TB occurs when tubercle bacilli are spread acutely though the blood stream. The symptoms are insidious at the onset with malaise, fever, anorexia and weight loss. In addition, headache from associated TB meningitis can occur with disseminated TB.

Signs and symptoms of central nervous system TB

Although only forming 5% of non-respiratory TB,{36} TB of the CNS is of disproportionate importance because of its significant morbidity and mortality. Early symptoms are non-specific with anorexia, malaise, headache, vomiting and altered behaviour. In children these can be poor feeding, irritability, altered behaviour, drowsiness or seizures. The prodromal phase can last from two weeks to two months, then focal neurological signs or decreasing level of consciousness occur. If cranial nerve palsies are present, 3rd and 6th nerve palsies are commoner than 7th and 8th nerve palsies. Internuclear ophthalmoplegia or lateral gaze palsies are less common but more serious because of midbrain or brainstem involvement.{37} Other neurological signs can develop depending on the site of endarteritis or infarction, including cerebellar signs, extrapyramidal movements such as choreoathetosis, hemiparesis or monoparesis.

Signs and symptoms of skin TB

Skin involvement can be due to disease of underlying structures, usually lymph node, bone or urogenital tract, with discharge through the skin, with sinus formation, so-called 'scrofuloderma'. Lupus vulgaris is a slowly destructive local skin form with dull red or violaceous edges. The tuberculides are forms of skin disease thought to be a manifestation of TB elsewhere in the body. Panniculitis, erythema induratum (Bazin's disease), and papular and papulo-necrotic forms are described and TB is in the differential diagnosis of such lesions, particularly in ethnic minority groups.{38}

Signs and symptoms of pericardial TB

TB can cause either pericardial effusion or constrictive pericarditis, particularly in ethnic minority groups. Fever, malaise, sweats, cough and weight loss can occur. The signs of pericardial effusion are oedema, pulsus paradoxus, a raised venous pressure, and hypotension with a narrow pulse pressure. With constrictive pericarditis, oedema, abdominal distension and breathlessness are the major signs and symptoms. A lymphocytic exudate on pericardial aspirate should be regarded as TB until proven otherwise.

Signs and symptoms of TB at other sites

TB should be considered in the differential diagnosis of adrenal deficiency, liver abscess, pancreatic mass in young adults with fever, and for isolated 'cold' abscesses wherever found, particularly in ethnic minority individuals.

Diagnosing active respiratory TB

The diagnosis of TB is suspected from a combination of context, symptoms, clinical signs and investigations. The diagnosis is rarely made from a single piece of evidence, and the sensitivity and specificity of individual tests may not reflect the strength of multiple tests or data. Most of the data on the utility of individual tests comes from studies in patients with proven tuberculosis by positive culture. Certain clinical settings are highly suggestive of tuberculosis in ethnic minority groups or recent TB contacts. These are: a pleural effusion which is a lymphocytic exudate, or isolated mediastinal lymphadenopathy, either supported by a positive skin tuberculin test (or IGT). These scenarios should be regarded as tuberculosis until proved otherwise and investigated accordingly.

A significant minority of respiratory TB cases however are not bacteriologically confirmed, but are treated on suspicion and regarded as probable cases because of response to specific anti-tuberculosis medication. The guideline aims to advise clinicians on which tests may help if cultures have been, or are subsequently shown to be, negative.

In children, who often have no culture confirmation, scoring systems have been developed to help diagnosis based on context, symptoms, X-ray appearances and other investigations. Some scoring systems are better validated than others.{39}

Diagnosing active non-respiratory TB

Most forms of non-respiratory tuberculosis have a lower bacterial load than for pulmonary disease, being so-called pauci-bacillary forms. A relatively very low proportion of cases have positive microscopy for acid-fast bacilli (AFB), and with the lower bacterial loads, even with rapid culture (see section 5.4) it takes longer to obtain positive cultures. With many of the non-respiratory sites, biopsy histology, or, in the case of lymph node disease, needle aspiration cytology, is available well before bacteriology. The finding of caseating granulomas, or granulomas with Langhan's giant cells on histology or cytology, is very highly suggestive of tuberculosis. A number of other conditions however can cause non-caseating granuloma formation. In the absence of caseation or Langhan's giant cells, additional tests such as a tuberculin skin test or IGT may be needed to assist in diagnosis. Obtaining a sample for culture is important as this confirms the diagnosis and provides the drug susceptibility profile of the organism. One caution is that in children aged under five, particularly if they are of white UK-born origin, granulomatous lymphadenitis is much more likely to be *M. avium* complex (MAC) than *M. tuberculosis*. To confirm this, samples are sent for culture, management for *M. avium* being completely different from *M. tuberculosis* in this context.{40}

The yield of histology/cytology depends on tissue sample size, which is much smaller with aspiration cytology than biopsy, and on the level of immune response which generates the histological appearances. In HIV-positive individuals the histological response depends on the level of immunosuppression. With levels of CD4 lymphocytes above 200/µl typical TB histology is the rule, but as the CD4 cell count falls, particularly below 100/µl, less and less granuloma formation occurs, and with profound immunosuppression there may be no cellular histological response at all. In these circumstances however there is an increased likelihood of AFB being seen microscopically. The differential diagnosis in such very immunosuppressed individuals is usually between *M. tuberculosis* and MAC infection. Polymerase chain reaction (PCR) techniques may help in distinguishing between these infections on AFB microscopy-positive samples (see section 5.3). A similar diagnostic problem can occur when patients with a very low CD4 count are started on highly active antiretroviral therapy (HAART). The rapid fall in HIV viral load and rise in CD4 count allows an immune response to be mounted to either of these organisms, which was

not previously possible. Enlargement of cervical and intra-abdominal lymph nodes in particular are described in this context, which is known as the immune reconstitution or IRIS syndrome.

In some cases of non-respiratory tuberculosis, the diagnosis of TB is not entertained in the differential diagnosis, and the doctor, usually a surgeon, does not send any material for culture, instead placing the entire sample in formalin. This then completely precludes any attempt at bacterial culture, although if AFB are seen histologically it still allows PCR-based techniques to be used (see section 5.3). The same histological and cytological criteria apply as in Table 27. Tuberculin skin tests or whole blood interferon-gamma based tests may be needed to assist with histological appearances that are not fully diagnostic.

5.2.2 Methodological introduction

Diagnosing active respiratory TB: testing while awaiting culture results

Studies were identified which calculated the sensitivity, specificity or predictive value of plain X-ray, sputum smear microscopy and gastric washings when compared with culture as the gold standard for the diagnosis of respiratory TB. Studies on sputum smear microscopy were excluded from review if they were conducted in non-Organisation for Economic Co-operation and Development countries as it was thought that in terms of background levels of mycobacteria and laboratory standards they might not be representative of the UK.

Eight studies examined the diagnostic accuracy of sputum smear microscopy in comparison with culture. Two US studies were excluded for methodological reasons.{41},{42}

Of the six remaining sputum microscopy studies, five were conducted in the US{43–47} and one in Turkey.{48} Three of these studies reported results for HIV-positive patients or those with AIDS.{43},{44},{47}

Four studies were identified which considered the diagnostic accuracy of chest X-ray in predicting culture results. One Danish study included all patients who had a respiratory sample examined for *M. tuberculosis* during a specified time period,{49}

a South African study was of paediatric patients suspected of having TB{50} whilst two US studies{51},{52} considered diagnostic accuracy of chest X-ray in those with AIDS/HIV.

Three studies considered the diagnostic accuracy of gastric washings in children.{53–55} Two of the studies were performed more than ten years ago in developing countries in populations with a high proportion of malnourished children, thus their applicability to the UK today is highly questionable. A more recent study performed in Cape Town, South Africa{55} compared gastric lavage and induced sputum samples from children in terms of their diagnostic yield, reporting how many cases were culture positive, smear positive or both.

Methodological considerations include the following:

- In terms of sputum smear microscopy, serial testing of sputum samples will increase the sensitivity and specificity of the test.
- Sensitivity and specificity values are calculated in different ways, either on a patient basis or a specimen basis.
- Methods used for processing the sputum specimen (including the minimum volume of sputum required and whether the specimen is expectorated or induced) or the method of isolating cultures may differ in various settings.

Generally studies were unblinded (mostly because they were retrospective analyses). Blinding, however, is probably not crucial to avoid bias in the assessment of smear microscopy as the same samples are used for smear and culture and are subject to standardised laboratory procedures and definitions. It was notable that none of the studies identified were performed in the UK.

Diagnosing active respiratory TB if culture results are negative

Two studies{56},{57} addressed the issue of what other test results might support a positive diagnosis in those with a negative culture for TB but with suspected respiratory TB. In a South African study a group of black male goldmine employees with small lesions in the lung apices on chest X-ray, and a positive skin test but negative sputum culture, were followed up.{56} A diagnosis of TB was made if the smear became positive, if the culture yielded *M. tuberculosis* or if a histological diagnosis was made. A Hong Kong study had a subgroup of patients who had TB

diagnosed on the basis of chest X-ray but had negative culture results.{57} This group were followed up for future confirmation of TB by culture of *M. tuberculosis* from sputum, or by radiographic or clinical deterioration.

Methodological issues for consideration are that the gold standard against which diagnostic tests for TB are usually compared is microbiological identification of TB by culture. This is not a perfect gold standard and culture might be negative in TB cases due to 'pauci-bacillary disease' (only a small number of *M. tuberculosis* organisms are present), sampling error or technical problems. In these cases where culture is negative, the standard against which a diagnostic test might be compared could be response to treatment, clinical features or a positive culture in the future. A TB diagnosis in this population would probably be achieved on a case-by-case basis and this has thus not been the subject of many studies.

Diagnosing active non-respiratory TB: testing while awaiting culture results
Studies were searched for which considered the sensitivity and/or specificity of histology from biopsy when compared with culture as the gold standard for the diagnosis of non-respiratory TB. Biopsies could be obtained during surgical procedures or by fine needle aspiration.

Four studies were identified where sensitivity of histology was calculated or it was possible to calculate sensitivity from the results reported. These studies were performed in India,{58} Malawi,{59} the USA{60} and the UK.{61} Two studies reported results in HIV-positive patients.{59},{60}

Due to the recognition that non-respiratory TB can have low positive culture rates, studies often base a firm TB diagnosis on histology or culture. A positive histology result is thus not necessarily considered to be inaccurate in the presence of a negative culture. For this reason, there are few studies which consider the sensitivity of histology from biopsy compared to culture alone as the reference standard. Studies merely report the numbers positive on each test. This is not useful for calculating the sensitivity of histology as it is necessary to know the results for each patient on both tests.

These studies were not blinded, mostly because they were retrospective analyses. The majority of specimens used in these studies were lymph nodes and little

information is available concerning whether sensitivity and/or specificity may differ when using specimens from other sites.

Although the diagnostic accuracy of individual tests was considered in isolation, in reality test results would not be considered in isolation but would contribute to the overall evidence on which a diagnosis is made.

Diagnosing active non-respiratory TB if culture results are negative

Studies of patients with suspected non-respiratory TB where the results of histology from biopsy or tuberculin skin test were used to support a positive diagnosis in those with a negative culture for TB were searched for.

As with respiratory TB, culture is not a perfect gold standard and may be negative in TB cases for several reasons. In particular in non-respiratory TB, this may be due to pauci-bacillary disease.

No studies were identified in culture-negative populations where the results of histology from biopsy or tuberculin skin tests were used to support a positive diagnosis.

5.2.3 Evidence statements: diagnosing active respiratory TB while awaiting culture results

Sputum microscopy

In a comparison in the USA{45} of direct and concentrated specimens, results were analysed for the first three sputum specimens received from patients who were culture-positive for *M. tuberculosis* and from whom three or more specimens were received. The cumulative proportion of positive smears for each of the three smears for concentrated specimens were 74%, 83% and 91% and this was 57%, 76% and 81% for direct smears. (**2**)

Sensitivity of smears (all smears, not per patient) using more than or equal to 5 ml of sputum volume in a study in the USA{46} was 92%. This was significantly greater than a sensitivity of 72.5% in a previous period when all specimens were processed regardless of volume. In both periods the specificity of acid-fast smear for *M. tuberculosis* was comparable at 98%. (**2**)

The rates of smear positivity were calculated for specimens of expectorated sputum, induced sputum and bronchoalveolar lavage (BAL) specimens in a study in the USA.{43} Findings of smears of expectorated sputum specimens showed that 55% were culture positive for *M. tuberculosis* and were AFB smear positive. Smear positivity rates for induced sputum were 38% and for BAL were 26%. When the predictive value was calculated by including only the first smear-positive specimen from each patient the values were 87% for expectorated sputum, 70% for induced sputum and 71% for BAL. (**2**)

A Turkish study{48} compared Ziehl-Neelsen (ZN) and fluorescence microscopy (FM) staining of sputum smears. Where only one specimen was submitted the sensitivities of ZN and FM stains were found to be 61% and 83% respectively. When two were submitted the sensitivities were 66% and 83% and where three or more were submitted sensitivities were 80% and 92%. (**3**)

In a US study{43} of expectorated sputum specimens that were culture positive for TB, 55% of specimens from both patients with and without AIDS (mean 2.4 specimens per patient for both groups) were smear positive. (**3**)

In a group of non-HIV infected, culture-positive TB patients in the USA,{47} 57% had positive acid-fast smears compared with 60% of the HIV-infected patients with culture-positive TB (all had at least three specimens tested). Among the TB culture-positive HIV-infected patients, no significant differences were found in the frequency of positive acid-fast sputum smears between groups stratified by CD4 cell counts (in those with a CD4 count of <50, 58% had positive smears, with a CD4 count of 50–200, 60% had positive smears and with a count of >200, 56% had positive smears). (**3**)

In a USA study,{44} 70% of all HIV-infected culture-positive TB patients and 71% of all non-HIV infected culture-positive TB patients had at least one positive smear (up to three were performed). The sensitivity for the diagnosis of TB dropped to 55% and 64% respectively when only the first smear was considered. (**3**)

Chest X-ray

According to X-ray category in a Danish study,{49} positive predictive values and sensitivity for TB were 61% and 67% respectively with X-ray changes thought to be

due to TB. These values were 20% and 19% with X-ray changes compatible with TB; 14% and 9% with previous TB and radiographically active TB; 2% and 3% with previous TB but not radiographically active TB and 1% and 2% with X-ray changes thought to be due to other disease. None of the patients with normal chest X-rays were culture positive. (**1**)

In a South African study{50} of the diagnostic accuracy of X-ray in children, the results yield a sensitivity of 38.8% and a specificity of 74.4% compared to culture for the diagnosis of pulmonary TB using standard radiographs. (**3**)

In a group of culture-positive adult AIDS patients a US study{51} found 36% of patients had a primary *M. tuberculosis* pattern, 28% had a post-primary *M. tuberculosis* pattern, 14% had normal radiographs, 13% had atypical infiltrates, 5% had minimal radiographic changes and 3% had a miliary pattern. Normal chest radiographs were seen for 10 (21%) of 48 patients with less than 200 T-cells per microlitre and one (5%) of 20 patients with more than 200 T-cells per microlitre ($p<0.05$). (**2**)

In a US study{52} of TB culture-positive adults, 78% of HIV-negative patients' radiographs were consistent with post-primary pattern TB versus 26% of patients who were HIV positive ($p<0.001$). Only 11% of 18 significantly immunosuppressed HIV-positive patients (CD4 counts <200) had X-rays consistent with post-primary pattern TB, while all four patients with CD4 counts >200 had typical post-primary pattern chest radiographs ($p<0.005$). Of the 16 significantly immunosuppressed HIV positive patients the predominant chest X-ray finding was diffuse or multilobar infiltrates without an upper lobe predominance (N=8) followed by normal chest X-ray (N=3). (**3**)

Gastric washings

In a study of Haitian children{54} the sensitivity, specificity and predictive value of positive fluorescence microscopy of gastric washings compared with culture were 58%, 95% and 81% respectively from 536 specimens (median three specimens per patient). Among 49 children with at least one positive fluorescence microscopy of gastric washings, pulmonary TB was bacteriologically confirmed in 85%. Specimens were more frequently positive in far-advanced and miliary disease (82%) than in less severe disease (32%) ($p<0.001$). (**3**)

Culture was grown in 16 gastric washings samples in a study of Indian children{53} and smears for AFB were positive in only three samples, thus sensitivity was 3/16 or 19% (most children had only one sample taken). (**3**)

A South African study{55} of children with suspected TB found that sensitivity of gastric lavage compared with culture was 39%, specificity was 99%, positive predictive value was 88% and negative predictive value was 90% (based on three gastric lavage samples). Similar results were found for induced sputum specimens, however the yield of culture positive cases from each method was 88% from induced sputum and 66% from gastric lavage. (**2**)

5.2.4 Evidence statements: diagnosing active respiratory TB if culture results are negative

In South African black male goldmine employees with small lesions in the lung apices on chest X-ray and positive skin tests but negative sputum culture, TB was subsequently diagnosed in 88 (58%) of the 152 men. A diagnosis of TB was made if the smear became positive or the culture yielded *M. tuberculosis* or if a histological diagnosis was made. Active TB developed in these men from three to 58 months after entering the study, with a mean of 19.8 months.{56} (**2**)

A study performed in Hong Kong of patients with TB diagnosed on the basis of chest X-ray, but with negative culture results, obtained eventual confirmation of active disease requiring treatment in 99 (57%) of 173 patients. During the first 12 months 43% had a confirmed diagnosis. Confirmation of TB was by culture of *M. tuberculosis* from sputum, or by radiographic or clinical deterioration. There was bacteriological confirmation in 41%. (**3**)

5.2.5 Evidence statements: diagnosing active non-respiratory TB while awaiting culture results

In patients who presented with lymphadenopathy in one or more extra-inguinal sites in Malawi{59} and who did not respond to general antibiotics, it could be calculated that the sensitivity of histology compared to culture was 70%, the specificity was 59%, the positive predictive value was 52% and the negative predictive value was 67%. (**2**)

In a US study{60} of lymph node specimens where the cytology report was compared with culture results, the sensitivity of cytology was calculated to be 72%. (**2**)

The sensitivity of histology (using a variety of specimens although most frequently lymph nodes) compared with culture in an East London population was 97% with a positive predictive value of 69%.{61} (**2**)

Where culture was the gold standard, an Indian study,{58} calculated that in clinically suspected cases of tuberculous lymphadenitis, sensitivity, specificity and positive predictive values for cytology were 78.5%, 73% and 76.7% respectively. (**1**)

HIV-positive

In a study in Malawi{59} in HIV-negative patients with TB lymphadenitis (diagnosed on the basis of a positive culture or histology result), 100% had positive histology results and 83% had positive culture results. These figures were 78% and 56% for those who were HIV positive. Thus the HIV status of the TB lymphadenitis patients suggests a negative influence of HIV infection on the possibility of both histology and culture being indicative of TB (OR 0.10, 95%CI 0 to 1.17, p=0.06). (**2**)

In a US study{60} of lymph node specimens where the cytology report was compared with culture results the sensitivity of cytology in those who were HIV negative was 76% and it was 69% in those who were HIV positive. (**2**)

5.2.6 From evidence to recommendations

The Chief Medical Officer's TB Action Plan{2} calls for primary and community care staff to be aware of 'the signs and symptoms of the disease, local TB services and local arrangements for referring patients with suspected TB'. As this guideline is aimed at generalist clinicians as well as those working regularly with people with tuberculosis, recommendations include signs, symptoms and potentially helpful imaging techniques. NICE guidelines generally do not include service guidance (although exceptions have been made elsewhere in this guideline), and so recommendations for local referral are not given.

The GDG were aware of the General Medical Council's advice{62} on gaining consent for testing for 'serious communicable diseases', but noted that this advice

was reprinted from prior guidance specific to HIV and did not feel that routine clinical practice supported it in TB, and that it was at variance with the Public Health Act.{63}

Testing for active respiratory TB while awaiting culture results

The yield of positive sputum microscopy is improved by an adequate sputum sample (5 ml or more), concentration of sputum, analysing multiple samples, and by fluorescence microscopy as the screening tool. Smear positive rates are higher for spontaneously induced sputum than for either induced sputum or BAL samples. The positive predictive value of positive sputum microscopy is 92% for spontaneously produced sputum, and 71% for both BAL and induced sputum. There appeared to be little difference in the results between HIV-positive and HIV-negative patients in terms of bacteriological results and sputum smear positivity. Microscopy on gastric washings has some utility in children, but a recent comparative study in children showed a single induced sputum (by hypertonic saline) to be superior to three gastric washings. Gastric washings are less likely to provide useful material in adults, because of acidic inhibition. Chest X-ray changes are less specific in children and HIV-positive individuals, particularly if the CD4 count is under 200 cells/µl.

Testing for active respiratory TB if culture results are negative

The evidence does not assess the adequacy of the respiratory samples sent for culture; a negative culture result can reflect no growth at that time, while a positive result may be obtained later. Chest X-ray appearances consistent with TB were noted to show progression to culture-proven disease in over 50% of subjects in the studies analysed from South Africa and Hong Kong. The decision whether to start TB treatment will be a clinical one based on experience, context and appraisal of all the individual's results. Further culture samples are sometimes needed after treatment has begun, and will remain viable for a few days, though growth may be slower; the GDG agreed a threshold of one week in this regard.

IGTs may also have a role in ruling out infection with *M. tuberculosis*; this area is developing rapidly and may need to be updated ahead of the rest of the guideline in 2008.

Testing for active non-respiratory TB while awaiting culture results

Microscopy can be strongly suggestive of TB with certain patterns, and this is often confirmed by a positive culture if material has been sent. Although the data were entirely for peripheral lymph nodes, the GDG thought that this was likely also to apply to other non-respiratory sites.

The decision to biopsy should not be influenced by concerns about sinus formation, as there is no evidence to support this with modern chemotherapy.

Patient preferences are an important consideration in choosing biopsy or needle aspiration.

Posterior–anterior chest X-rays in people with suspected non-respiratory disease are helpful through detecting any coexisting respiratory disease, which will aid or confirm the diagnosis, and be another potential source of bacteriological confirmation. The GDG also agreed a range of other potential tests and imaging techniques.

Testing for active non-respiratory TB if culture results are negative

Although there was no evidence in this area, the GDG noted that continuous enhanced surveillance by the Health Protection Agency (HPA) shows that only some 55% of cases of TB are culture confirmed, and that this is often because no samples have been obtained, with the diagnosis being entirely histological. (However, other reasons include failures in the reporting system and limitations of the matching between Enhanced Tuberculosis Surveillance and MycobNet systems.) To raise the proportion of TB cases diagnosed, particularly at non-respiratory sites, more samples from common TB sites should be sent for TB bacteriology, which requires the education of those sending samples such as general, ENT and orthopaedic surgeons and radiologists performing biopsies.

IGTs may also have a role in ruling out infection with *M. tuberculosis*; this area is developing rapidly and may need to be updated ahead of the rest of the guideline in 2008.

5.2.7 RECOMMENDATIONS

R19 To diagnose active respiratory TB:

- a posterior–anterior chest X-ray should be taken; chest X-ray appearances suggestive of TB should lead to further diagnostic investigation C(DS)
- multiple sputum samples (at least three, with one early morning sample) should be sent for TB microscopy and culture for suspected respiratory TB before starting treatment if possible or, failing that, within seven days of starting C(DS)
- spontaneously produced sputum should be obtained if possible; otherwise induction of sputum or bronchoscopy and lavage should be used B(DS)
- in children unable to expectorate sputum, induction of sputum should be considered if it can be done safely, with gastric washings considered as third line B(DS)
- if there are clinical signs and symptoms consistent with a diagnosis of TB, treatment should be started without waiting for culture results (see section 6.1 for details) D(GPP)
- the standard recommended regimen should be continued in patients whose subsequent culture results are negative D(GPP)
- samples should be sent for TB culture from autopsy samples if respiratory TB is a possibility. D(GPP)

R20 To diagnose active non-respiratory TB:

- advantages and disadvantages of both biopsy and needle aspiration should be discussed with the patient, with the aim of obtaining adequate material for diagnosis B(DS)
- if non-respiratory TB is a possibility, part or all of any of the following samples should be placed in a dry pot (and not all placed in formalin) and sent for TB culture: D(GPP)
  - lymph node biopsy
  - pus aspirated from lymph nodes
  - pleural biopsy
  - any surgical sample sent for routine culture
  - any radiological sample sent for routine culture
  - histology sample
  - aspiration sample

  - autopsy sample
- microbiology staff should routinely perform TB culture on the above samples (even if it is not requested) D(GPP)
- the appropriate treatment regimen should be started without waiting for culture results if the histology and clinical picture are consistent with a diagnosis of TB (see chapters 6 and 7) C(DS)
- all patients with non-respiratory TB should have a chest X-ray to exclude or confirm coexisting respiratory TB; in addition, tests as described in Table 27 should be considered D(GPP)
- the appropriate drug regimen (see chapters 6, 7 and 9) should be continued even if subsequent culture results are negative. D(GPP)

Table 27: Suggested site-specific investigations in the diagnosis and assessment of non-respiratory TB

Site	Imaging	Biopsy	Culture
Lymph node		• Node	• Node or aspirate
Bone/joint	• Plain X-ray and computed tomography (CT) • Magnetic resonance imaging (MRI)	• Site of disease	• Biopsy or para-spinal abscess • Site or joint fluid
Gastrointestinal	• Ultrasound • CT abdomen	• Omentum • Bowel	• Biopsy • Ascites
Genitourinary	• Intravenous urography • Ultrasound	• Site of disease	• Early morning urine • Site of disease • Endometrial curettings

2006

Disseminated	• High resolution CT thorax • Ultrasound abdomen	• Lung • Liver • Bone marrow	• Bronchial wash • Liver • Bone marrow • Blood
Central nervous system	• CT brain • MRI	• Tuberculoma	• Cerebrospinal fluid (CSF)
Skin		• Site of disease	• Site of disease
Pericardium	• Echocardiogram	• Pericardium	• Pericardial fluid
Cold/liver abscess	• Ultrasound	• Site of disease	• Site of disease

2006

Cross-referring:

For details of rapid diagnostic tests, see sections 5.3 and 5.4.

For people with active TB, see treatment under chapters 6, 7 and 9.

For details of contact tracing, see section 12.2.

For details of notification and enhanced surveillance, see chapter 14.

5.3 Rapid diagnostic tests: molecular methods

5.3.1 Clinical introduction

Molecular probes for diagnosis

A number of methods have been developed which target and amplify specific regions of mycobacterial DNA, thus allowing a rapid result. However, such tests can result in false negative and false positive findings. Although rare, false positive results may occur due to contamination of the sample with environmental mycobacteria causing non-specific binding to the probe. More commonly, false negative results may occur due to low organism numbers or, in some sample types, for example CSF, to the presence of inhibitors. The specificity and sensitivity of the tests has been compared with culture proven disease. However, since 20–30% of

pulmonary cases, and a higher proportion of non-pulmonary cases are not culture proven, the performance of molecular tests in these settings is difficult to assess.

Molecular probes for species confirmation

Species identification may sometimes be possible directly from the specimen using the techniques referred to above. Most usually, this will be possible only for *M. tuberculosis* complex organisms (*M. tuberculosis*, *M. bovis*, *M. africanum*). However, these methods may allow early differentiation between these organisms and environmental mycobacteria. These tests are most effective when applied to samples in which mycobacteria have been detected microscopically. Their use is currently recommended, to confirm true tuberculosis (ie transmissible disease) before a large contact tracing exercise, for example in a school or hospital, is carried out.{6}

When a sample yields a positive culture, rapid identification of several commonly encountered species may be possible. This may be done by the application of an expanded range of DNA amplification-based assays or by the use of non-amplified hybridisation probes. Both of these approaches are effective since the high numbers of organisms present in a positive culture overcome the problems associated with low bacterial counts and inhibition in the primary sample. The Mycobacterium Reference Service of the HPA now routinely confirms to clinicians whether a positive culture received is from the *M. tuberculosis* complex or not.

Molecular probes for rifampicin resistance

The incidence of multi-drug resistant strains of *M. tuberculosis* (MDR TB) in the UK is low (~1%) (see Appendix G). However, in some areas of the country and in some population groups the incidence is much higher. Whilst it should be noted that mono-resistance to rifampicin is found in approximately 5% of rifampicin-resistant strains, a high proportion of rifampicin resistance is associated with concurrent resistance to isoniazid (~95%). Thus the detection of resistance to rifampicin can be used as a marker for MDR TB with a high level of accuracy.

Rifampicin resistance is commonly due to one or more of several possible mutations of the *rpo*B gene and these can be detected using a PCR-based technique. A positive result from such a test should lead to the implementation of infection control measures and drug treatment for MDR TB until the results of

standard drug susceptibility tests are available. Risk factors for MDR TB, which should lead to such tests for rifampicin resistance, are listed in section 9.1. Clinicians should be aware that there is a small (<5%) false negative rate for these tests as a few mutations conferring rifampicin resistance are not at the *rpo*B gene tested for.{64},{65}

Molecular typing of M. tuberculosis isolates

In the past the typing of *M. tuberculosis* strains has been principally to detect previous events. This was largely due to the comparatively slow techniques available (for example, restriction fragment length polymorphisms). Newer methods based on the detection of variable numbers of tandem repeat sequences within the *M. tuberculosis* genome (variable number of tandem repeats (VNTR)/mycobacterial interspersed repetitive unit (MIRU) typing) are amenable to automation. As a result rapid, high-throughput typing systems have become available. These systems also have the advantage of digitised data which allow much easier computerised storage and analysis than previous typing methods. If this rapidity of method is used to type strains as they are isolated, then potential links between patients may be detected early enough to interrupt the disease transmission process. Thus an epidemiological tool may make an impact on diagnosis and transmission.

5.3.2 Methodological introduction

In consideration of the use of molecular methods for rapid diagnosis of TB, the review being developed by the NHS Heath Technology Assessment Programme{66} has been adopted. This aims to conduct a systematic review of the effectiveness of available diagnostic tests to identify mycobacteria. The review is not yet published.

The draft review of nucleic acid amplification tests (NAAT) found 163 studies which compared NAAT with a reference standard. There were 105 comparisons in respiratory specimens and 67 in non-respiratory specimens. In these studies 77 of the tests used were commercially produced (the amplified *Mycobacterium tuberculosis* direct (AMTD) test, the Amplicor, the Ligase Chain Reaction and Ampicis Myco B) and 86 were produced in-house (insertion element IS6110 or other targets).

Methodological issues concern the complexity of pooling data from diagnostic studies in particular due to variation in diagnostic thresholds. Furthermore, studies report pairs of related summary statistics (sensitivity and specificity) rather than a single statistic, requiring alternative statistical methods for pooling results. This review presents diagnostic odds ratios (DOR) in addition to sensitivity and specificity data. This is a single summary of diagnostic performance which although not easy to apply in clinical practice (it describes the ratio of the odds of a positive test result in a patient with disease compared to a patient without disease) is convenient to use when combining studies as it is often fairly constant regardless of diagnostic threshold. The DOR can be calculated from sensitivity and specificity data and where a test provides no diagnostic evidence the DOR is 1. It has been suggested{67} that a DOR of 25 or more in a test may provide convincing diagnostic evidence.

5.3.3 Evidence statements

The health technology appraisal (HTA) on rapid diagnostic tests{66} is not yet published. The GDG considered interim results, reporting the DOR statistic calculated by comparing NAAT *vs*. a reference standard. All evidence is graded at level 2.

5.3.4 From evidence to recommendations

Molecular probes for diagnosis

The HTA of rapid tests showed that their sensitivity was equivalent to culture in microscopy negative pulmonary samples, but there was an increased false negative rate in non-respiratory samples, particularly in pleural fluid and CSF. Significant false negative rates in these settings limit their utility, and could lead to failure to diagnose and treat TB.

Molecular probes for species confirmation

The GDG did not look into the HTA's interim results for molecular probes, but noted their role in rapid confirmation. They were not felt to be more reliable or useful than culture confirmation, and use was therefore limited to occasions when a rapid decision is needed on treatment or infection control measures. A further role was in preventing large scale contact tracing exercises from starting unnecessarily.

Molecular tests are less feasible on poorer samples, and the recommendations given below advise on their use on biopsy material.

Molecular probes for rifampicin resistance

Again, the GDG recognised the advantages of rapid results for drug resistance, but noted that MDR TB risk factors should be used to determine infection control measures at the earliest opportunity.

Molecular typing of M. tuberculosis isolates

Although this has not been subject to formal HTA appraisal, these methods have been considered by the HPA and a unified strategy using a 15 locus VNTR/MIRU system agreed. Such a strategy was recommended in the TB Action Plan.{2}

5.3.5 RECOMMENDATIONS

R21 Rapid diagnostic tests for *M. tuberculosis* complex *(M. tuberculosis, M. bovis, M. africanum)* on primary specimens should be used only if: D(GPP)

- rapid confirmation of a TB diagnosis in a sputum smear-positive person would alter their care, or
- before conducting a large contact-tracing initiative.

R22 Clinicians should still consider a diagnosis of non-respiratory TB if rapid diagnostic tests are negative, for example in pleural fluid, CSF and urine. B(DS)

R23 Clinical signs and other laboratory findings consistent with TB meningitis should lead to treatment (see section 7.1), even if a rapid diagnostic test is negative, because the potential consequences for the patient are severe. D(GPP)

R24 Before conducting a large contact-tracing initiative (for example, in a school or hospital), the species of *Mycobacterium* should be confirmed to be *M. tuberculosis* complex by rapid diagnostic tests on microscopy- or culture-positive material. Clinical judgement should be used if tests are inconclusive or delayed. D(GPP)

R25 If a risk assessment suggests a patient has MDR TB (see section 7.1): D(GPP)

- rapid diagnostic tests should be conducted for rifampicin resistance
- infection control measures and treatment for MDR TB should be started as described in chapter 9, pending the result of the tests.

R26 Rapid diagnostic tests for *M. tuberculosis* complex identification should be conducted on biopsy material only if: D(GPP)

- all the sample has been inappropriately placed in formalin, and
- AFB are visible on microscopy.

Cross-referring:

For details of managing drug-susceptible TB, see chapters 6 and 7.

For details of managing drug-resistant TB, see chapter 9.

5.4 Rapid diagnostic tests: automated liquid culture

5.4.1 Clinical introduction

Clinicians have been advised to obtain culture confirmation of tuberculosis whenever possible.{68} This not only confirms the diagnosis, but crucially also obtains material for drug susceptibility testing, which is important because of the current levels of drug resistance in England and Wales. The finding of isoniazid resistance (currently 6% of isolates) requires modification of treatment (see section 9.4), and that of MDR TB (currently about 1% of isolates) different infection control procedures (see section 9.3) and individualised treatment regimens based on the drug susceptibility data.

Until recently, culture for mycobacteria was done mainly on solid media, the Lowenstein-Jensen slope, or in broth media. These methods were slow, with cultures from microscopy positive material taking from 2–4 weeks, and for microscopy negative material 4–8 weeks. More recently rapid culture methods have been developed, with the potential advantages of more rapid growth and hence earlier drug susceptibility data, and also possibly increased sensitivity.

The national TB Action Plan has as one of its aims the use of rapid culture methods for diagnosis of all cases of tuberculosis.{2}

5.4.2 Methodological introduction

The reduced turnaround time of automated liquid culture in comparison with solid media is uncontested. In addition to time to detection of mycobacteria, study outcomes in comparisons between solid and liquid media also report increases

recovery rates for mycobacteria.{66} Sensitivity and or specificity cannot be reported in these studies as there is no reference standard.

There were no studies identified which directly addressed the issue of when (ie in what circumstances) automated liquid culture methods for the diagnosis of TB are most useful.

The HTA on rapid diagnostic techniques{66} is not yet published. The GDG considered interim findings on liquid culture techniques.

5.4.3 From evidence to recommendations

Given the evidence base and the self-evident speed of automated liquid culture, the GDG recommended their universal use.

Liquid culture methods require batches of samples to be processed. Their use becomes more costly per test if fewer samples are processed at any one time by a laboratory. The batching of samples sent to regional laboratories may not reflect future service organisation as this technology becomes more widely used over the lifetime of this guideline, but the recommendations allude to the effect of throughput on efficiency, quality control and cost-effectiveness. The NICE guideline, in the absence of clinical evidence, is unable to recommend service configurations to address this, though the GDG considered a 'hub and spoke' arrangement of regional laboratories.

5.4.4 RECOMMENDATIONS

R27 Clinical samples should ideally be sent for culture by automated liquid methods, bearing in mind that laboratories need a certain level of throughput to maintain quality control. D(GPP)

6 Management of respiratory tuberculosis

6.1 Drug treatment

6.1.1 Clinical introduction

Respiratory TB is defined as active TB affecting any of the following:

- lungs
- pleural cavity
- mediastinal lymph nodes
- larynx.

Duration of treatment

Six months of daily treatment with rifampicin and isoniazid, supplemented in the initial two months with pyrazinamide and either ethambutol or streptomycin (the six-month four-drug regimen) has been the evidence-based gold standard for TB treatment for at least the last 15 years. No new first-line drugs have been found for over 30 years. Attempts have been made to shorten the total duration of treatment by reducing the duration of the continuation phase of treatment. The comparators for such studies are the results of the six-month, short-course, four-drug regimen, which give a cure and completion rate of >95% and a relapse rate of 0–3% in both clinical trial{69} and routine clinic use.{70},{71} Such controlled studies have been largely conducted in adults not known to be HIV positive, with a few in HIV-positive individuals or in children.

Dosing schedule

Trials have also been conducted on reduced treatment frequency, comparing a daily dosing schedule with higher dosages of drugs given twice or thrice weekly. The aims of these studies were to reduce the total number of doses taken, as both an aid to adherence and treatment monitoring, and to reduce the costs of treatment in resource-poor countries. Intermittent treatment can be given either throughout the initial and continuation phases, or intermittently through the continuation phase after a daily intensive initial phase. Certain drug side effects (for example, 'flu-like syndrome', thrombocytopenia, shock and acute renal failure) are more common when rifampicin is given intermittently rather than daily, and are immunologically mediated. Twice- or thrice-weekly regimens lend themselves more readily to DOT as they require less frequent monitoring of medication, reducing the costs of supervision if done in a healthcare setting.

Combination medicines

Adherence with drug treatment is a major determinant of the outcome of treatment.{72} As an aid to adherence, combination tablets of three drugs (rifampicin, isoniazid and pyrazinamide) are available for use in the two-month initial

phase of treatment, and of two drugs (rifampicin and isoniazid) in the four-month continuation phase of treatment. The dosages in combination tablets however are those set for a daily dosing schedule. The other potential advantage of combination tablets is that they prevent accidental or inadvertent single drug therapy which can lead to acquired drug resistance within weeks in active TB disease. Care however is needed in the prescribing and dispensing of TB drugs in the UK, because of the similarities in names between several of the drugs (see Table 28).

Table 28 Commonly confused generic and brand names

Drug(s)	Brand name
Rifampicin (called rifampin in USA)	Rimactane, Rifadin
Rifabutin	Mycobutin
Rifampicin + isoniazid	Rifinah, Rimactazid
Rifampicin + isoniazid + pyrazinamide	Rifater
Isoniazid	Rimifon (not marketed in UK)
Ibuprofen	Rimafen

Enlarged hilar lymph nodes in children

Children with enlarged hilar lymph nodes that cause bronchial compression and collapse with respiratory distress frequently benefit from additional glucocorticoid therapy, although the evidence is limited.{73}

6.1.2 Current services

Dedicated TB clinics

In all parts of the country, over half of TB service providers taking part in our review of current services (see section 2.8) had a dedicated TB clinic. The percentage was 64% in London and 53% elsewhere in England and Wales. There may be a trend for these to be sited in services with a higher caseload of active TB (shown by number of notifications), but this is not reflected in caseload of screening (number of people screened). Screening is sometimes reported being carried out in a separate clinic, but it is not possible from our data to conclude whether or not there is consistency (or benefit) in having a combined approach.

This guideline recommends culturally relevant, practical and sensitive advice for patients, involving them in treatment decisions, and having a designated key worker they can contact. Bringing the TB service together in the framework of a dedicated clinic is one way to help the team achieve this. However, it is understandable that it will not be justified in all localities.

Nurse-led follow-up clinics

The review of current services found that outside London, 31% of TB service providers had nurse-led follow-up clinics. The majority of these conducted some follow up at the patient's home. In London, 55% of TB service providers had nurse-led follow-up clinics. None of these followed up patients at home. Variation in the provision of these nurse-led follow-up clinics did not seem to be explained by the caseload (notifications), staffing levels or presence of specialist personnel. It is impossible to conclude from our data whether the variation is appropriate to local epidemiology, geography or service models, but these are all factors that ought to have been considered in the design of the TB service.

Specialist TB+HIV clinics

The review of current services found that, outside London, only 5 of 60 (8%) participating service providers reported a specialist joint TB+HIV clinic, although in three cases this was a service by HIV physicians with TB nurse input. Five other clinics reported access to such specialist clinics elsewhere. In London, 10 of 33 (30%) service providers had a specialist TB+HIV clinic, although five other clinics reported access to these specialist clinics. Outside London, these specialist TB+HIV clinics tended to be sited in areas with higher numbers of notifications.

Specialist paediatric TB clinics

The review of current services revealed a few different models for providing paediatric TB care. Children were seen by respiratory or paediatric doctors with, in some cases, TB nurse input. In one clinic, generalist paediatric doctors ran a service for BCG, and treatment of active and latent TB with TB nurse input.

The number and proportion of service providers running clinics with specialist TB nurse input was 11 (17%) outside London, and 21 (64%) in London. Four other service providers, one outside London and three in London had access to these clinics. In two places outside London, the clinics were community paediatric clinics, and one was a hospital paediatric/BCG clinic. In 22 (34%) outside London, and three (9%) in London, patients were seen in paediatric clinics without TB nurse input. In 27 service providers outside London and six in London, patients were seen either by a respiratory physician, or the responsible healthcare professional was not recorded.

Access to specialist paediatric clinics seemed to predominate in areas of higher caseload outside London, but this distinction was less apparent within London. Variation in the provision of paediatric specialist services did not seem to be explained by staffing levels or the presence of specialist personnel. Given the special considerations required for diagnosing and treating TB in children, as well as providing advice to parents, it is important that adequate specialist expertise is available to the TB service. The above service models represent different ways of approaching this where caseload justifies a specific service model.

Outreach work

The review also looked into outreach in patients' homes and other community settings. This is reported in detail under section 8.3.

6.1.3 Methodological introduction

Duration of treatment

A Cochrane systematic review{74} assessed the effects of regimens lasting less than six months, compared to any longer regimens in the treatment of active TB (eg studies could compare two months *vs*. four months or five months *vs*. eight months). Seven trials were included (three trials in India,{75–77} two trials in Hong Kong,{78},{79} one trial in Singapore{80} and one in Germany{81}) and five of these studies compared regimens of less than six months with regimens of six months or more.

An additional RCT{82} was identified which compared a five-month regimen with a twelvemonth regimen. However, this was excluded due to methodological limitations.

No studies were found comparing treatment regimens of less than six months with longer durations in HIV-infected adults or in children.

A major consideration is that although these studies were very large (4,100 patients included in total), they did not perform intention to treat analyses and thus relapse rates are based only on study participants who complied fully with the treatment protocol (having taken at least 75–90% of scheduled treatment).

Dosing schedule

A Cochrane systematic review{83} compared the effectiveness of rifampicin-containing short-course treatment regimens, given twice or thrice weekly, with similar regimens given daily in adult patients with pulmonary TB. Only one RCT performed in Hong Kong was included within the review.{84} The review{83} was methodologically sound; however as it only included one study, this was reviewed separately. This RCT{84} was excluded due to limitations in its methodology.

The Cochrane review included studies where the intermittent arm was any rifampicin-containing multiple drug regimen with a maximum nine month duration, administered up to three times a week with an initial daily dosing phase which could not exceed one month (this was termed 'fully intermittent'). Three further RCTs{85–87} and a cohort study{88} were identified using similar inclusion criteria, except in terms of the initial daily dosing phase which was broadened to cover studies where this could be two months long, in line with the usual initial intensive treatment phase. Studies could also be intermittent during the intensive phase. The cohort study{88} and one RCT{87} were excluded due to methodological limitations.

In terms of HIV-infected populations and children, a US cohort study{89} in an HIV-infected population was identified but excluded on the basis of limitations in the methodology, as was an RCT which compared twice-weekly and daily chemotherapy in children with respiratory TB.{90} No further studies were identified in either of these populations.

None of the studies identified were blinded. Certainly this may have been problematic to achieve in terms of study participants, however those assessing outcomes could potentially have been blinded to treatment allocations.

Very few studies have compared intermittent regimens with daily regimens. Where studies have been conducted, apart from issues of methodology, there are a number of other variables which should be considered when attempting to compare studies and ascertain whether intermittent and daily regimens have equivalent effectiveness. These include whether the intermittent treatment was received during the intensive or continuation treatment phases or during both, the drugs and dosing regimens used, whether treatment was directly observed or self-administered and the frequency of the intermittent regimen (ie whether once, twice or thrice weekly).

There is little high-quality evidence in this area and none of the studies identified were performed in the UK. In particular, no robust evidence is available in HIV-positive individuals or children.

Combination medicines

Six RCTs compared fixed dose combination tablets with single-drug formulation regimens.{91–96} All of the studies except one used a fixed dose combination tablet containing isoniazid, rifampicin and pyrazinamide. The exception was an Indonesian study{96} which compared a four-drug, fixed-dose regimen containing isoniazid, rifampicin, pyrazinamide and ethambutol with single-drug formulations.

Four of the studies were excluded due to methodological limitations.{91},{92},{94},{95}

Two studies were included, one preliminary study from Indonesia{96} and one study from China,{93} which followed patients up for two years to assess relapse. In both of these studies treatment was directly observed in all patients, which is not a standard service model in the UK.

6.1.4 Evidence statements

Duration of treatment

A Cochrane systematic review{74} of seven RCTs compared regimens of six months or less with any longer regimens (thus not necessarily six months or longer). For those with active TB, relapse rates were significantly better in the longer groups of the meta-analyses of two months (OR 6.1, 95%CI 2.19 to 17.01), three months (OR 3.67, 95%CI 2.42 to 5.58) and four months (OR 3.64, 95%CI 1.71 to 7.75) of treatment *vs*. longer treatment, but not in the single trial of five *vs*. seven months. Relapse rates after longer (comparison) regimens ranged from 0–7% at one year (or more) and in the shorter treatment arms they ranged from 2–20% (the two highest rates of 18% and 20% being in the three-month regimen). (**1+**)

When only regimens of less than six months were compared with durations of six months or longer, relapse rates were significantly lower in the regimens of six months or more, for three months *vs*. six months (OR 15.61, 95%CI 4.97 to 49.04), three months *vs*. 12 months (OR 5.11, 95%CI 1.37 to 19.08), and four months *vs*.

2006

six months (OR 3.64, 95%CI 1.71 to 7.75) but not in the five *vs*. seven months comparison.{74} (**1+**)

There was little or no difference in the rates of adverse reactions or toxicity requiring a change or discontinuation of treatment when comparing regimens of six months or less with longer regimens and few or no deaths were reported in individual trials. Furthermore, the 'sterilising efficacy' (sputum culture negative immediately after the completion of treatment) varied little among treatments, providing no predictive value for relapse rates.{74} (**1+**)

Dosing schedule

In a RCT performed in Africa and Asia,{86} a significantly higher proportion of patients assigned a directly observed daily regimen in the two-month intensive phase rather than a directly observed three times weekly regimen, were culture negative at two months (85% *vs*. 77%, p=0.001). (**1++**)

In a Brazilian RCT{85} there was no significant difference between self-administered six-month treatment regimens, where treatment was daily for the first two months and then either daily or twice weekly during the continuation phase, in terms of the number of bacterial failures or deaths during treatment. (**1+**)

The same study{85} also found no significant difference between daily and twice-weekly regimens in the continuation phase of treatment in terms of adherence (measured by pill counts), relapse rates at 12 months follow up or adverse events. (**1+**)

Combination medicines

An Indonesian study{96} compared a four-drug, fixed-dose combination (isoniazid, rifampin, pyrazinamide and ethambutol) with the same drugs in separate formulations and found there was no significant difference in terms of sputum conversion at two months or cure, failure or defaulter rates. The difference in frequency of complaints during the intensive phase between the separate and combined drugs groups was significant in terms of gastrointestinal complaints (56% *vs*. 41% respectively, p<0.01) and muscle joint complaints (46% *vs*. 32% respectively, p=0.01). (**1+**)

In a comparison in China{93} of a six-month, three-drug, fixed-dose combination tablets (isoniazid, rifampin, pyrazinamide) regimen with the same drugs in separate formulations, at the end of two and six months of treatment, the bacteriological status of patients did not differ significantly in the two treatment groups as determined by examination of both sputum smear and culture. Bacterial relapse in those who completed treatment at two years was not significantly different between the two groups. 11.8% of patients in the combined drug group, and 15.5% of patients in the separate drugs group, experienced adverse reactions, most of which were insignificant and temporary. Patients in the combined drug group actually took 99.9% of their treatment doses whilst in the separate drug group, 97% of doses were taken. (**1+**)

6.1.5 From evidence to recommendations

Specialised clinical staff are central to good management of TB, as has been shown in audit results.{97},{98}

The Cochrane review of this area includes trials in adults not known to be HIV positive. Few data are available in either HIV-positive adults or in children, but the Cochrane review's conclusions should be applicable.

The increasing rates of isoniazid resistance seen in the epidemiology of England and Wales (see Appendix G) led the GDG to recommend a standard six-month, four-drug initial treatment regimen. Two studies have looked into the effect of this regimen in clinical settings in the UK and shown it to be effective and safe across susceptible and isoniazid-resistant strains.{99}

No studies compared twice- or thrice-weekly treatment with daily treatment throughout a six-month regimen, but nevertheless the GDG agreed that twice- and thrice-weekly regimens, with appropriate dosage adjustments, are effective in the treatment of tuberculosis. A single-arm, twice weekly regimen, using rifabutin in HIV-positive individuals with active tuberculosis in the USA (CDC TB Trials Consortium Trial Number 23), was stopped because of the development of acquired rifamycin resistance.{100} In addition to this concern, the twice-weekly regimen is the absolute minimum dosage strategy, and the penalty of missed doses may be

increased relapse or treatment failure. For this reason the thrice-weekly regimen, which has a greater safety margin for a few missed doses, is recommended.

Whilst being easier to supervise twice- or thrice-weekly treatment, the large number of different pills (necessarily given as separate formulations), particularly in the initial four-drug phase, can cause nausea and adversely affect adherence. Vomiting as a side effect of rifampicin can be reduced at dosages of 600 mg or more by being taken after breakfast. Flu-like syndromes are more common with intermittent as opposed to daily rifampicin treatment.

The dosages of combination tablets are set for once-daily treatment.

The cost to the patient of prescription charges is lower for combination tablets.

Few studies in the evidence base for combination medicines are free from methodological limitations. Only one study used the three-drug combination available in the UK.{93} Virtually all the data are from adult patients not known to be HIV positive, but the GDG felt that the conclusions can be extrapolated to children and HIV-positive individuals.

Given the benefits of combination tablets, and the key aim of treatment completion and adherence, the GDG recommended them.

6.1.6 RECOMMENDATIONS

R28 Once a diagnosis of active TB is made, the clinician responsible for care should refer the person with TB to a physician with training in, and experience of, the specialised care of people with TB. The TB service should include specialised nurses and health visitors. TB in children should be managed either by a paediatrician with experience and training in the treatment of TB, or by a general paediatrician with advice from a specialised physician. If these arrangements are not possible, advice should be sought from more specialised colleagues throughout the treatment period. C

R29 A six-month, four-drug initial regimen (six months of isoniazid and rifampicin supplemented in the first two months with pyrazinamide and ethambutol) should be used to treat active respiratory TB in:

- adults not known to be HIV positive. A
- adults who are HIV positive. B
- children. B

This regimen is referred to as 'standard recommended regimen' in this guideline.

R30 Fixed-dose combination tablets should be used as part of any TB treatment regimen. C

R31 A thrice-weekly dosing regimen should be considered for patients receiving DOT (see section 8.2). D(GPP)

R32 A twice-weekly dosing regimen should not be used for the treatment of active TB. D(GPP)

Cross-referring:
For details of DOT, see section 8.2.
For details of approaches to improve adherence, see section 8.3.
For details of managing drug-resistant TB, see chapter 9

6.2 Infection control

6.2.1 Clinical introduction

It has long been recognised that people who are sputum microscopy positive from spontaneously expectorated sputum are those cases with the highest infectivity, and pose a risk to household and other close contacts such as workplace contacts. For these reasons, traditionally, patients with pulmonary disease in whom tuberculosis is suspected are isolated in a single room. This isolation has been recommended until three separate sputum tests have been analysed. If these sputum tests are negative, the patient is usually deemed to pose a significantly lower infection risk. They may then be moved from the single room to a shared ward, provided there are no HIV-positive or other patients with major immunocompromise on the same ward. If patients are sputum microscopy positive, having so-called 'open' tuberculosis, and need to be admitted to hospital, isolation is required until treatment makes the person non-infectious.{101},{102} Such drug

treatment causes an extremely rapid fall in viable organisms in the sputum, even if AFB are still visible on microscopy.

Current clinical practice has been based on the 2000 BTS Joint Tuberculosis Committee guidance, which supported nursing adults with non-pulmonary tuberculosis on a general ward. However, aerosol-generating procedures such as abscess or wound irrigation are carried out in separate facilities.

6.2.2 6.2.2 Methodological introduction

Studies were searched for that focussed on measures directed at patients with infectious TB to prevent transmission to other patients or contacts. It was expected that these measures might include mask wearing by the patient, isolation in a single room, negative pressure rooms, germicidal ultraviolet radiation or air disinfectant at sites of transmission.

There were few studies which considered TB transmission to other patients or contacts rather than healthcare workers when assessing the effectiveness of infection control measures. This is likely to be due to healthcare workers having regular Mantoux tests tests available for analysis, the fact that healthcare workers are easier to follow up than patients and because employers must consider TB as an occupational hazard. Furthermore, studies tended to look at infection control in MDR TB rather than drug-susceptible TB patients. This seems to be because infection control measures were implemented in several hospitals in the USA after MDR TB outbreaks in the late 1980s and early 1990s.

Additional considerations are that the quality of the infection control measures, for example the level of negative pressure in a negative pressure isolation room, may vary over time.

Furthermore, infection control measures are often implemented together, which makes it difficult to assess the contribution of each measure.

One US study{103} without a comparison group that considered hospital transmission of TB among patients after the implementation of infection control measures was identified. This was excluded on the basis of methodological limitations.

No further studies were found that assessed the effects of infection control on patient TB transmission rates in either HIV-positive or negative patients, therefore it was not possible to write evidence statements.

6.2.3 From evidence to recommendations

The GDG felt there was no good evidence to support measures for infection control in patients with smear-positive disease not suspected to have MDR TB, whether or not HIV positive, and endorsed the guidance given in the BTS guideline.{68}

It is important to prevent unnecessary hospitalisation, as this is one of the major cost drivers for TB treatment. Treatment can proceed in the patient's home, considering that the household members will be contacted through contact tracing, and that infectiousness declines rapidly once treatment begins.

When children with TB are admitted to hospital, it is important to consider their visitors as likely close contacts, and to screen them when they visit as part of contact tracing, and also as infection control.

Given the unexpected data on negative pressure facilities from the review of current service (see 9.3.2), and similar findings in other surveys, the recommendations spell out the three categories of infection control, and require simple steps to clarify which rooms meet the agreed standards.

There can be conflicting guidance on whether staff should wear masks. It was agreed that masks are only required for MDR TB or during close contact in cough-inducing procedures, for example bronchoscopy and sputum induction. Patients are reassured by effective infection control measures, but are also often worried unnecessarily by masks or gowns, especially if these steps are not explained to them. The only role for patients wearing masks was within the first two weeks of treatment (when the patient remains infectious) and when they are outside their single room, for example going for an X-ray (as they may come into contact with other, susceptible, patients).

Readers should be aware of relevant guidance available from the Health and Safety Executive.{104}

6.2.4 RECOMMENDATIONS

The recommendations below deal with three levels of isolation for infection control in hospital settings:

- *negative pressure rooms, which have air pressure continuously or automatically measured, as defined by NHS Estates*{105}
- *single rooms that are not negative pressure but are vented to the outside of the building*
- *beds on a ward, for which no particular engineering standards are required.*

R33 All patients with TB should have risk assessments for drug resistance (see section 9.1) and for HIV. If risk factors for MDR TB are present, see section 9.3 for recommendations on infection control. D(GPP)

R34 Unless there is a clear clinical or socioeconomic need, such as homelessness, people with TB at any site of disease should not be admitted to hospital for diagnostic tests or for care. D(GPP)

R35 If admitted to hospital, people with suspected respiratory TB should be given a single room. D(GPP)

R36 Patients with respiratory TB should be separated from immunocompromised patients, either by admission to a single room on a separate ward, or in a negative pressure room on the same ward. D(GPP)

R37 Any visitors to a child with TB in hospital should be screened as part of contact tracing, and kept separate from other patients until they have been excluded as the source of infection. D(GPP)

R38 Smear-positive TB patients without risk factors for MDR TB (see section 9.1) should be cared for in a single room, until: D(GPP)

- they have completed two weeks of the standard treatment regimen (see section 6.1), or
- they are discharged from hospital.

R39 Aerosol-generating procedures such as bronchoscopy, sputum induction or nebuliser treatment should be carried out in an appropriately engineered and ventilated area for: D(GPP)

- all patients on an HIV ward, regardless of whether a diagnosis of TB has been considered
- all patients in whom TB is considered a possible diagnosis, in any setting.

R40 Healthcare workers caring for people with TB should not use masks, gowns or barrier nursing techniques unless: D(GPP)

- MDR TB is suspected
- aerosol-generating procedures are being performed.

When such equipment is used, the reason should be explained to the person with TB. The equipment should meet the standards of the Health and Safety Executive. See section 9.3 for further details of MDR TB infection control.

2006

R41 TB patients admitted to a setting where care is provided for people who are immunocompromised, including those who are HIV-positive, should be considered infectious and, if sputum smear-positive at admission, should stay in a negative pressure room until: D(GPP)

1. the patient has had at least two weeks of appropriate multiple drug therapy, *and*
2. if moving to accommodation (inpatient or home) with people who are immunocompromised, including those who are HIV-positive, the patient has had at least three negative microscopic smears on separate occasions over a 14-day period, *and*
3. the patient is showing tolerance to the prescribed treatment and an ability and agreement to adhere to treatment, *and either*
4. any cough has resolved completely, *or*
5. there is definite clinical improvement on treatment, for example remaining afebrile for a week.

For people who were sputum smear negative at admission (that is, three negative samples were taken on separate days; samples were spontaneously produced

2006, amended 2011

sputum if possible, or obtained by bronchoscopy or lavage if sputum samples were not possible): *all* of 1, 2, 3 and 5 above should apply.

R42 Inpatients with smear-positive respiratory TB should be asked (with explanation) to wear a surgical mask whenever they leave their room until they have had two weeks' drug treatment. D(GPP)

Cross-referring:

For details of managing drug-resistant TB, see chapter 9.

For details of contact tracing among hospital inpatients, see section 12.7.

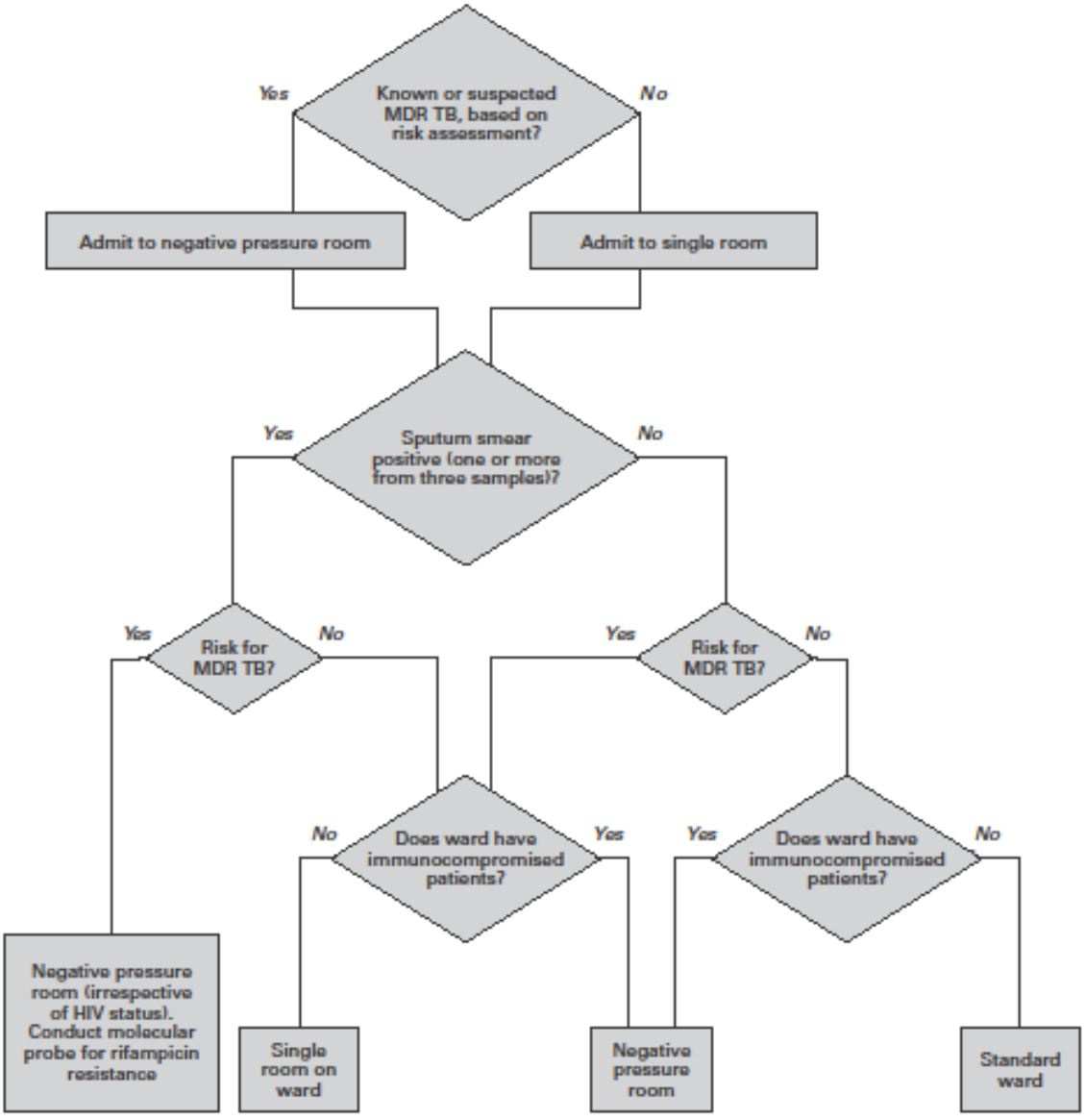


Figure 2: Algorithm showing isolation decisions for patients with suspected respiratory TB

7 Management of non-respiratory tuberculosis

7.1 Meningeal tuberculosis

7.1.1 Clinical introduction

Tuberculous meningitis occurs when there is blood-borne spread of the TB bacteria to the brain. In the days before treatment was available this usually occurred within 12 months of the original (primary) infection.{106} It is sometimes part of a more widespread blood-borne dissemination, with chest X-ray patterns typical of miliary tuberculosis.{107} It can present with systemic features if due to miliary disease, or more local central nervous system signs if limited to the brain. Unlike acute bacterial meningitis with, for example, the meningococcus, the onset of TB meningitis is insidious over a few weeks. In infants there may be non-specific symptoms such as not feeding or a failure to thrive. There can be headache and vomiting, then increasing drowsiness, and localised neurological signs such as cranial nerve palsies or hemiparesis, progressing to coma.

Clinically, the meningitis is classified according to the following stages:

- stage I: no clouding of consciousness or focal neurological signs
- stage II: clouding of consciousness and/or focal neurological signs
- stage III: coma.{108}

The diagnosis is supported by lumbar puncture suggesting CSF changes: a low glucose, raised protein and a lymphocyte dominant pattern of white blood cells. Diagnosis is confirmed by demonstrating *M. tuberculosis* on microscopy or culture of the CSF, or demonstrating *M. tuberculosis* DNA by PCR testing. TB meningitis may be accompanied by tuberculomas, inflammatory masses in the brain, which can either be present at diagnosis on CT brain scan or develop during treatment.{109} Although only approximately 100 cases of TB meningitis occur in England and Wales each year, this form of TB has a high morbidity and mortality when compared to nearly all other forms of non-respiratory tuberculosis.{110} Disability and death can still occur despite early diagnosis and appropriate treatment.

7.1.2 Methodological introduction: duration of treatment in adults

Studies were included where the majority of patients were adults (16 years of age and over) and where a modern drug treatment regimen was used to treat TB meningitis. Thus, treatment had to include at least isoniazid, rifampicin and pyrazinamide.

Two cohort studies performed in Turkey{111} and Thailand{112} were identified which compared different durations of treatment for TB meningitis. Two case series performed in Thailand{113} and Ecuador{114} and one treatment arm of a study performed in India{115} were also considered. All of the studies were completed more than 15 years ago and were excluded due to methodological limitations.

There is a lack of high-level evidence in this area. There are no RCTs which compare different durations of treatment for TB meningitis and there are no good quality cohort studies. This seems to be due to the relative rarity of the condition (small patient numbers in studies) and the associated high mortality and morbidity. The studies that do exist are plagued by a number of methodological problems including small sample size, a lack of generalisability due to completion in developing countries, patients in variable stages of clinical severity, problems with definitive diagnosis of TB meningitis, concurrent use of glucocorticoid therapy and a lack of inferential statistics. Due to the low quality of the studies in this area, it was not possible to write evidence statements.

7.1.3 Methodological introduction: duration of treatment in children

One systematic review of case series studies{116} was identified. This compared studies of six months treatment duration for TB meningitis with those of more than six months treatment duration. Nine studies were included, four of which were in the six months duration group{113},{114},{117},{118} and five in the more than six months duration group.{111},{119–123} Approximately 75% of the patients included were children. The review had several methodological limitations and due to these issues, the studies included in this review and performed in children were assessed separately. These were two studies performed in India,{120},{122} one in Thailand{117} and another in South Africa;{118} however all of these studies were excluded on the basis of methodological limitations.

Within the area of treatment duration for TB meningitis in children (as with adults) there is a lack of high-level evidence. Studies had similar methodological limitations to those in adult populations. Additionally, the issue of generalisability of results to the UK was even more marked as one study reported high levels of childhood malnutrition.{122} Due to the low quality of the studies in this area, it was not possible to write evidence statements.

7.1.4 Methodological introduction: glucocorticoids as an adjunct to antituberculous drugs

A Cochrane systematic review{124} compared the effects of glucocorticoids in combination with anti-TB treatment with anti-TB treatment alone in patients with TB meningitis. The review consisted of six RCTs{125–130} and was methodologically sound and hence it could technically be given a grading of 1++/1+. However, the methodological limitations of individual studies contained within the review meant that there was insufficient robust data from which to derive evidence statements. The authors of the review concluded that

'adjunctive steroids might be of benefit in patients with TB meningitis. However, existing studies are small, and poor allocation concealment and publication bias may account for the positive results found in this review'.

In the study steroids were associated with fewer deaths (RR 0.79, 95%CI 0.65 to 0.97) and a reduced incidence of death and severe residual disability (RR 0.58, 95%CI 0.38 to 0.88). Subgroup analysis suggested an effect on mortality in children (RR 0.77, 95%CI 0.62 to 0.96) but the results in a smaller number of adults were inconclusive (RR 0.96, 95%CI 0.50 to 1.84).

Another systematic review{131} was also appraised; however this was excluded due to methodological limitations.

One further RCT was identified.{132} This was a very high-quality study performed in Vietnam in adults and included patients who were HIV positive.

Studies were excluded where glucocorticoids were administered intrathecally as this rarely occurs due to the necessity of a lumbar puncture. This was the approach taken in the Cochrane systematic review.{124}

Due to the methodological issues associated with the studies in the Cochrane review{124} there is no sound evidence available for the use of corticosteroids in children with TB meningitis. There is also no compelling evidence in this area for HIV-positive patients.

7.1.5 Evidence statements

Mortality and severe residual disability

In a RCT performed in Vietnam{132} in TB meningitis patients over 14 years of age, adjunctive treatment with dexamethasone was associated with a reduced risk of death (RR 0.69, 95%CI 0.52 to 0.92, p=0.01). It was not however associated with a significant reduction in the proportion of severely disabled patients or in the proportion of patients who either died or were severely disabled after nine months.{132} (**1++**)

Disease severity and HIV status

The treatment effect of adjunctive dexamethasone was consistent across subgroups that were defined by:

- disease severity grade (stratified RR of death, 0.68, 95%CI 0.52 to 0.91, p=0.007){132}
- HIV status, although the reduction in the risk of death was not significant (the number of HIV-infected patients was too small to confirm or reject confidently a treatment effect).{132} (**1++**)

Adverse effects

Significantly fewer serious adverse events occurred in the dexamethasone group than in the placebo group (26 of 274 patients *vs*. 45 of 271 patients, p=0.02). In particular eight severe cases of hepatitis (one fatal) occurred in the placebo group and none occurred in the dexamethasone group (p=0.004).{132} (**1++**)

7.1.6 From evidence to recommendations

The evidence base in this area is hampered by the difficulty of recruiting patients for participation in studies. Mostly the existing studies included people following a presumptive diagnosis with few positive culture confirmations.

There is no evidence to support treatment durations of less than 12 months, but all the evidence on duration has some methodological limitations. Given the serious

risk of disability and mortality, the advice given in the 1998 BTS guidelines{68} remains appropriate.

There is also no evidence to inform the choice of drugs. Caution is required with ethambutol in unconscious patients, streptomycin should be avoided in pregnancy if at all possible (fetal 8th nerve damage) and there is potential teratogenicity with ethionamide and prothionamide.{133}

The important factor in drug choice was penetration into CSF. Ethionamide, isoniazid, prothionamide and pyrazinamide achieve best penetration. Rifampicin is less good in this regard, and ethambutol and streptomycin only penetrate into CSF if the meninges are inflamed.

Given the potential severe effects of neurological damage arising from TB meningitis, and the strong evidence in adults from the Vietnam study{132} supporting additional glucocorticoids, this guideline recommends them. There is no reason to give a high-dose glucocorticoid to most patients, and the GDG reached a consensus on reviewing treatment response after 2–4 weeks with a view to starting to withdraw the glucocorticoid as soon as it is safe to do so.

7.1.7 RECOMMENDATIONS

R43 Patients with active meningeal TB should be offered:

- a treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (for example, ethambutol) for the first two months, followed by isoniazid and rifampicin for the rest of the treatment period D(GPP)
- a glucocorticoid at the normal dose range
  - adults equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg. A
  - children equivalent to prednisolone 1–2 mg/kg, maximum 40 mg D(GPP)

with gradual withdrawal of the glucocorticoid considered, starting within 2–3 weeks of initiation. D(GPP)

R44 Clinicians prescribing treatment for active meningeal TB should consider as first choice:

- a daily dosing schedule B
- using combination tablets. D

Cross-referring:
For details of standard drug treatment, see section 6.1.
For details of managing drug-resistant TB, see chapter 9.

7.2 Peripheral lymph node tuberculosis

7.2.1 Clinical introduction

Lymph node TB is an important form of non-respiratory TB accounting for nearly half of all non-respiratory sites{26},{27} (see epidemiology in Appendix G). Since non-respiratory disease is found less commonly in white UK-born people than in others, who now make up nearly 70% of all cases in the UK, the number of cases of lymph node disease seen is rising.

Trials by the BTS and its predecessors with regimens of 18 months,{134} nine months{134},{135} and six months duration,{135–137} all showed a significant proportion of cases (up to 40%) to have residual nodes at the end of treatment, and up to 10% at 30 month follow-up. Sometimes new nodes and occasionally sinuses develop during treatment and/or during follow-up. Nearly all of these events are thought to be immunologically mediated responses to residual tuberculo-proteins, and not failure to respond to treatment or relapses. When cultured there is seldom evidence of bacteriological activity.

7.2.2 Methodological introduction

A meta-analysis{138} of studies of varying designs compared six-month treatment regimens with nine month regimens in people with peripheral lymph node TB. However, this was excluded due to methodological limitations.

Two RCTs identified in the meta-analysis were assessed seperately.{137} One UK trial comparing six months *vs.* nine months daily treatment was reported in two papers firstly as preliminary results{136} and then follow-up results at 30 months.{137} The other trial performed in Hong Kong{139} compared six months

and nine months thrice-weekly treatment, however this was excluded due to limitations in methodology.

There was a lack of high-quality comparative studies in this area, thus only one has been included as evidence.{136},{137}

7.2.3 Evidence statements

A UK RCT{136},{137} of patients with peripheral lymph node TB compared two nine-month drug regimens (2HRE/7HR and 2HRZ/7HR) and one six-month regimen (2HRZ/4HR). Of those patients seen at 30 months (85%), there was no statistically significant difference between the groups in terms of reported residual measurable nodes, relapse, enlargement of existing nodes, development of new glands or sinuses or the need for new operative procedures. Aspiration after commencement of treatment was performed in eight patients: seven on the 2HRE/7HR regimen and the other on 2HRZ/4HR (2HRE/7HR versus all HRZ, p=0.005). (**1+**)

7.2.4 From evidence to recommendations

There was little evidence to guide the GDG in more practical issues, but it was felt that treatment should be stopped at the end of the regimen regardless of the appearance of new nodes, residual nodes or sinuses draining.

One study{136},{137} of six months *vs.* nine-months treatment duration shows equivalence for fully susceptible organisms. However, this trial used a three-drug initial phase (2RHZ), which may be inadequate in view of current drug resistance rates,{140} and the isoniazid resistance rate of 12% in the trial.{136},{137} The standard six-month, four-drug regimen is therefore recommended.

Drug treatment is still required even if a gland has been surgically removed, because of the possibility of residual local and distal TB foci. Surgical excision biopsy for histology and culture is advised if pus cannot be aspirated from a gland. Fine needle aspiration does not give adequate samples for TB culture.

7.2.5 RECOMMENDATIONS

R45 For patients with active peripheral lymph node tuberculosis, the first choice of treatment should:

- be the standard recommended regimen (see section 6.1 for further details) B

- use a daily dosing schedule B
- include combination tablets. D

R46 Patients with active peripheral lymph node TB who have had an affected gland surgically removed should still be treated with the standard recommended regimen. D(GPP)

R47 Drug treatment of peripheral lymph node TB should normally be stopped after six months, regardless of the appearance of new nodes, residual nodes or sinuses draining during treatment. D(GPP)

Cross-referring:
For details of standard drug treatment, see section 6.1.
For details of managing drug-resistant TB, see chapter 9.

7.3 Bone and joint tuberculosis: drug treatment

7.3.1 Clinical introduction

Spinal TB accounts for approximately half of all the sites of bone and joint TB seen in England and Wales.{22},{26},{27} As such it is an important subset of non-respiratory disease, and one which can sometimes have significant morbidity because of spinal cord compression from extradural abscess and/or vertebral collapse. For these reasons, the GDG considered the evidence base on the medical management of spinal TB as a proxy for the management of the many possible joint sites, in which separate drug trials have not been conducted.

7.3.2 Methodological introduction

Three RCTs were identified which compared different durations of treatment in those with TB of the spine.

A Hong Kong study{141} with fourteen years of follow-up compared six, nine and eighteen months of treatment in those who had undergone radical anterior resection with bone grafting. The results of this trial (without the 18 month arm) were also reported at five years in a paper that presented the results of two further trials at five years in Madras and Korea,{142} which both compared six months of treatment with

nine months in patients who had not received surgery. The Madras trial was also reported with follow-up at ten years.{143} The Korean trial{142} was excluded due to a number of methodological limitations.

These trials were all originally commenced in the 1960s and 1970s by the British Medical Research Council (MRC) and although they subscribed to the methodological standards of the time, they do not include all patients in the analyses in the groups to which they were originally allocated (ie an intention to treat analysis). In line with NICE guidance in circumstances where an intention to treat analysis has not been used and there is little evidence available, these studies have been evaluated as if they were non-randomised cohort studies.

These studies did not use the standard, four-drug initial treatment regimens currently used in the UK and none of the studies reported blinding methods.

7.3.3 Evidence statements

In a Hong Kong study{142} at five years follow-up, all analysed patients who had received radical anterior resection with bone grafting and a six- or nine-months treatment regimen of isoniazid, rifampicin and streptomycin (except one in each group) had favourable status at five years, and most had achieved favourable status by three years. (Favourable status was defined as full physical activity with radiographically quiescent disease, with neither sinuses nor clinically evident abscesses and with no myelopathy with functional impairment and no modification of the allocated regimen). (**2+**)

In the Hong Kong study{141} at 14 years follow-up, clinical outcomes were similar in the six-, nine-and 18-month treatment regimen groups. One patient in the six months group had minor motor deficits whereas one patient in the 18 months group had partial unilateral sensory deficits. No patients had bladder or bowel disturbances at final follow-up and there was no recurrence or reactivation of tuberculosis in either group. Additionally there were no statistically significant differences in the change in mean angle of deformity between the groups and most side effects occurred early in treatment and were not related to duration of treatment. (**2+**)

In a study in Madras{142} of patients who received treatment (isoniazid and rifampicin) without surgery for six or nine months, 91% in the six-month group and 98% in the nine-month group had a favourable status at five years (using the same definition as the Hong Kong study{142}). At ten years{143} there was no significant difference in favourable status, or occurrence of complete bony fusion. The angle of kyphosis increased in both regimens with no significant difference between groups; however, in patients less than 15 years of age with angle of kyphosis >30°, the mean increase by ten years was 30°, compared with 10° in those >15 years (p=0.001). (**2++**)

7.3.4 From evidence to recommendations

A number of trials were conducted in association with the British MRC between the 1960s and 1980s in Korea, India and Hong Kong, designed according to the standards of the time. Whilst they did not use intention to treat analysis, these studies on six, nine and 18 months of treatment, with extensive follow-up of up to 10 years in some cases, show that six months duration of treatment performed just as well as longer regimens. The GDG agreed that these results are likely to be applicable to other forms of bone and joint tuberculosis, and accordingly recommended the standard six-month, four-drug regimen.

The GDG acknowledged the risk of CNS involvement via the spinal cord, and recommended scans to check for any patient with neurological signs or symptoms. The was no evidence to guide a choice of either CT or MR scanning.

7.3.5 RECOMMENDATIONS

R48 The standard recommended regimen (see section 6.1 for details) should be planned and started in people with:

- active spinal TB B
- active TB at other bone and joint sites. C

R49 Clinicians prescribing treatment for active bone and joint tuberculosis should consider as first choice:

- a daily dosing schedule B
- using combination tablets. D

See section 6.1 for details.

R50 CT or MR scan should be performed on patients with active spinal TB who have neurological signs or symptoms. If there is direct spinal cord involvement (for example, a spinal cord tuberculoma), management should be as for meningeal TB (see section 7.1). D(GPP)

Cross-referring:
For details of managing drug-resistant TB, see chapter 9.

7.4 Bone and joint tuberculosis: routine therapeutic surgery

7.4.1 Clinical introduction

From before the age of anti-tuberculosis treatment, immobilisation and bed rest were thought to be important for bone and joint tuberculosis. This view continued after the development of anti-tuberculosis drugs and into the time when shorter durations of treatment with newer drugs were available. A series of studies by the MRC, commencing in 1965, showed the respective roles of anti-tuberculosis treatment and other routine management measures in spinal tuberculosis. Studies in Korea found no benefit from routine bed rest,{144},{145} or of a plaster jacket during therapy,{145},{146} and in Rhodesia no benefit from routine initial debridement of lesions.{147} Prior to the introduction of rifampicin, trials of radical anterior fusion showed mixed results.{142},{148–151} The advent of rifampicin led to further trials on the use of anterior spinal fusion in conjunction with short-course treatment regimens.

7.4.2 Methodological introduction

Two RCTs were identified which compared surgery and drug treatment for those with TB of the spine with drug treatment alone.

A study in Rhodesia{149} compared debridement and drug treatment with drug treatment alone but was excluded for methodological issues.

A Madras study, reporting at five{142} and ten years,{143} compared radical resection with bone grafting plus six months' treatment with isoniazid and rifampicin with just six or nine months' treatment with isoniazid and rifampicin.

The Madras trial, whilst in line with the methodological standards at the time it was commenced, did not include all patients in the analysis in the group to which they had been originally allocated (ie an intention to treat analysis). In line with NICE guidance in circumstances where an intention to treat analysis has not been used and there is little evidence available, these studies have been evaluated as if they were non-randomised cohort studies. Furthermore, it should be noted that a two-drug regimen would not now be used in the UK as standard therapy.

7.4.3 Evidence statements

At five years,{142} radical resection with bone grafting in addition to six-months treatment regimen (with isoniazid and rifampicin) showed no benefit in status (favourable status was defined as no sinus or clinically evident abscess, no myelopathy and no modification of allocated regimen, no limitation of physical activity due to spinal lesion and radiologically quiescent disease) compared to six- or nine-months treatment regimen alone. (**2++**)

Whilst at ten years,{143} the surgery and six-months treatment regimen was less effective in terms of favourable status than the nine-month treatment regimen alone ($p=0.03$), the difference being due to surgical complications. However, patients in the surgery and anti-tuberculosis drug treatment group had a faster resolution of sinuses and/or clinically evident abscesses ($p<0.001$ at two months) and a lower incidence ($p=0.03$) than those in the anti-tuberculosis drug treatment only groups. There was no significant differences found between the groups in terms of occurrence of complete bony fusion or angle of kyphosis. There were four deaths associated with spinal tuberculosis (all within the first six months and all in the surgery and anti-tuberculosis drug treatment group). Three died in the postoperative period and the other had complications of postoperative paraplegia. (**2++**)

7.4.4 From evidence to recommendations

Although the GDG concluded that the evidence showed no additional advantage of routinely carrying out anterior spinal fusion over standard chemotherapy, the

recommendations for spinal surgery cannot be extrapolated to bone/joint tuberculosis at other sites.

Aspiration of paraspinal abscesses and/or biopsy from spinal sites may be needed for the diagnosis of TB, which is different from routine anterior fusion. Forms of surgery such as aspiration or arthroscopy of joints may be needed to obtain material for histology and culture by which to make the diagnosis of tuberculosis in bone/joint sites other than the spine.

7.4.5 RECOMMENDATIONS

R51 In patients with spinal TB, anterior spinal fusion should not be performed routinely. B

R52 In patients with spinal TB, anterior spinal fusion should be considered if there is spinal instability or evidence of spinal cord compression. D(GPP)

7.5 Pericardial tuberculosis

7.5.1 Clinical introduction

TB of the pericardium accounts for less than 4% of non-respiratory TB in England and Wales,{140} but is potentially important because of the possibilities of cardiac tamponade and constrictive pericarditis, which have a mortality and morbidity higher than most other forms of extrapulmonary TB.

The presence of a pericardial effusion may require aspiration by pericardiocentesis for diagnosis, repeated during treatment. Similarly, considerable pericardial thickening, with or without fluid, may require surgery with pericardectomy or a pericardial window, which is a major invasive intervention. Additional glucocorticoids tailing from the equivalent of prednisolone 60 mg/day have been recommended in the UK,{68} following studies in Transkei, South Africa, where this form of active tuberculosis was particularly common,{152},{153} which appeared to show reduced morbidity and mortality.

7.5.2 Methodological introduction

A Cochrane systematic review{154} attempted to compare six-month anti-tuberculosis drug treatment regimens with regimens of nine months or more in

people with tuberculous pericarditis. The Cochrane review search did not identify any RCTs which compared anti-tuberculosis drug regimens of these different durations.

No further studies were identified which compared six months of treatment with longer treatment durations, thus it was not possible to write evidence statements on the duration of treatment for TB pericarditis.

Two systematic reviews, which considered the effectiveness of glucocorticoids in addition to drug treatment in patients with TB pericarditis were identified. A Cochrane systematic review{154} considered this issue in addition to a number of other treatment issues in TB pericarditis (treatment duration, pericardial drainage and pericardectomy) whilst a review by the same authors, published elsewhere, only considered the issue of additional glucocorticoids for TB pericarditis.{155} The same four studies were included in both reviews{152},{153},{156},{157} and the results presented and the publication year were the same.

The two RCTs included in these reviews by Strang{152},{153} have since been reported at ten years.{158} Results from this new report which now includes an intention to treat analysis, along with the two other RCTs identified in the systematic reviews, have thus been considered separately. One of these studies was excluded on methodological grounds.{156} The other study included HIV-positive patients only.{157}

TB pericarditis is relatively rare and so it is difficult to find enough patients to study; furthermore, it is also difficult to diagnose. For example, the study in HIV patients{157} was small (N=58) and the TB diagnosis was confirmed by culture in only 38% of the participants.

7.5.3 Evidence statements

The results of RCTs performed in Transkei, South Africa, comparing prednisolone to placebo in pericardial effusion and pericardial constriction patients with or without drainage are presented in the table below.{158}Table 29 also includes the results of an RCT comparing prednisolone *vs*. placebo in HIV-positive pericardial effusion patients.{157}

Table 29 Summary of evidence for pericardial TB

TB pericardial effusion without open drainage	**Evidence**
	• Prednisolone reduced the need for repeat pericardiocentesis, which was required in 10% of prednisolone patients and 23% of placebo patients (p=0.025).{158}
	• Adverse outcomes of any type were significantly less frequent in the prednisolone than the placebo group, occurring in 19% compared with 40% respectively (p=0.003).{158}
TB pericardial effusion with/without open drainage	**Evidence**
	• Adverse outcomes occurred in 52% with neither open drainage nor prednisolone, *vs*. 14% drainage and prednisolone, 11% drainage and placebo and 19% prednisolone and no drainage (p=0.08 for interaction).{158}
TB pericardial effusion HIV positive	**Evidence**
	• Survival was significantly improved in the prednisolone group compared with the placebo group when patients were followed up for 18 months (p=0.004). However, although steroids were associated with fewer deaths, this was not statistically significant if the timing of the deaths was not taken into account (RR 0.5, 95%CI 0.19 to 1.28).{157}
	• Improvement in physical activity (p=0.02) and resolution of raised jugular venous pressure (p=0.017), hepatomegaly (p=0.007) and ascites (p=0.051) were faster in prednisolone-treated patients than those given placebo.{157}
	• There was no difference in the rate of radiologic and echocardiographic resolution of pericardial effusion, the risk of constrictive pericarditis or the frequency of steroid-related complications between the prednisolone and placebo groups.{157}
TB pericardial constriction	**Evidence**
	• There were no significant differences in adverse outcomes or deaths from pericarditis between prednisolone and placebo groups.{158}
Any pericarditis	**Evidence**
	• In a multivariate survival analysis (stratified by type of pericarditis), prednisolone reduced the overall death rate after adjusting for age and sex (p=0.044) and substantially reduced the risk of death from pericarditis (p=0.004).{158}

7.5.4 From evidence to recommendations

The group were not aware of any further evidence on the treatment regimen and concluded that first-line treatment is with the standard six-month, four-drug regimen.

There are no comparative studies on which to base recommendations on the duration of treatment. Since this is a pauci-bacillary form of extrapulmonary disease by extrapolation from other forms of extrapulmonary disease with more evidence, a six-month duration of treatment is expected to be effective.

The GDG agreed that the RCT evidence{157},{158} strongly supported the use of glucocorticoids in adults with active pericardial tuberculosis and that they were also likely to be beneficial in children.

7.5.5 RECOMMENDATIONS

R53 For patients with active pericardial TB, the first choice of treatment should:

- be the standard recommended regimen (see section 6.1 for details) B
- use a daily dosing schedule B
- include combination tablets. D

R54 In addition to anti-TB treatment, patients with active pericardial TB should be offered:

- for adults, a glucocorticoid equivalent to prednisolone at 60 mg/day. A
- for children, a glucocorticoid equivalent to prednisolone 1 mg/kg/day (maximum 40 mg/day)

with gradual withdrawal of the glucocorticoid considered, starting within two to three weeks of initiation. D(GPP)

Cross-referring:
For details of managing drug-resistant TB, see chapter 9.

7.6 Disseminated (including miliary) tuberculosis

7.6.1 Clinical introduction

In the 1997 guidance on notification, it was suggested that those with non-specific symptoms started on TB treatment should be described as having 'cryptic disease' with the term 'cryptic miliary disease' being reserved for those where the organism has been isolated from blood, from bone marrow or from multiple organ systems. In clinical texts there is usually a distinction between 'classical miliary' disease with the diffuse 1–2 mm uniform micronodular chest X-ray from acute haematogenous

spread which may also involve other organs, including the CNS, and 'cryptic miliary' where the patient may have fever but few localising signs. The data collection form for enhanced TB surveillance gives possible sites of TB, including miliary and cryptic disseminated. Cryptic disseminated is defined as 'systemic illness without localising features'.

These different labels for forms of what is essentially blood-borne spread of tuberculosis can cause confusion. Essentially, blood-borne spread may or may not be accompanied by chest X-ray or high-resolution CT changes. Such blood-borne spread often also causes significant liver function derangement because of diffuse liver involvement. This is a serious form of TB with a significant morbidity and mortality, so the risks of treating the disease with drugs which have a low incidence of hepatic side effects (3%), are much less than those of leaving the patient inadequately treated. The meninges are also not infrequently involved as part of the blood-borne spread, with up to 30% having clinical or lumbar puncture evidence of such involvement.{140} The detection of CNS disease is important because of the longer duration of treatment required for CNS involvement.

7.6.2 Methodological introduction

One retrospective study{159} where patients with disseminated TB received three different durations of treatment was identified, however this was excluded due to small sample size (N=6).

No other comparative studies were found, hence it was not possible to write evidence statements.

7.6.3 From evidence to recommendations

No data were found to inform recommendations. It is noted that all sites outside the CNS for which data exist show adequate response to a six-month, four-drug initial treatment regimen, but that six-month regimens have not been shown to be adequate for those with CNS involvement (see section 7.1).

Exclusion of CNS disease is important, by CT scan, MRI or lumbar puncture, so that the correct duration of treatment is applied.

Abnormal liver function should not prevent or delay the commencement of TB treatment, which usually causes improvement in liver function abnormalities due to the disease itself.

7.6.4 RECOMMENDATIONS

R55 For patients with disseminated (including miliary) TB, the first choice of treatment should:

- be the standard recommended regimen (see section 6.1 for details) B
- use a daily dosing schedule B
- include combination tablets. D

R56 Treatment of disseminated (including miliary) TB should be started even if initial liver function tests are abnormal. If the patient's liver function deteriorates significantly on drug treatment, advice on management options should be sought from clinicians with specialist experience of these circumstances. D(GPP)

R57 Patients with disseminated (including miliary) TB should be tested for CNS involvement by:

- brain scan (CT or MRI) and/or lumbar puncture for those with CNS signs or symptoms
- lumbar puncture for those without CNS signs and symptoms.

If evidence of CNS involvement is detected, treatment should be the same as for meningeal TB (see section 7.1). D(GPP)

Cross-referring:
For details of managing drug-resistant TB, see chapter 9.

7.7 Other sites of infection

7.7.1 From evidence to recommendations

There is no evidence base available to derive recommendations for other sites of infection. However, as the pathogen and its drug susceptibility is the same, treatment has generally been given with the same regimen as is used for respiratory

tuberculosis. The GDG's clinical experience supported this and hence the recommendation below is extrapolated from the evidence base for respiratory tuberculosis, and other non-respiratory sites.

7.7.2 RECOMMENDATION

R58 For patients with:

- active genitourinary TB, or
- active TB of any site other than:

– respiratory system
– CNS (typically meninges)
– peripheral lymph nodes
– bones and joints
– pericardium
– disseminated (including miliary) disease

the first choice of treatment should:

- be the standard recommended regimen (see section 6.1 for details) B
- use a daily dosing schedule B
- include combination tablets. D

Cross-referring:
For details of managing drug-resistant TB, see chapter 9.

8 Monitoring, adherence and treatment completion

8.1 Treatment completion and follow-up

8.1.1 Clinical introduction

In the UK, when the recommended regimen has been given to patients with fully susceptible organisms, the rate of relapse is low (0–3%) in both trial{69} and clinical practice conditions,{160} if there has been good adherence with treatment. Under these circumstances, it is important to know whether routine follow-up after treatment completion is cost-effective in detecting relapse.

8.1.2 Methodological introduction

No studies were identified which compared the detected relapse rates of previously treated TB patients who were subject to routine follow-up, with a group who did not receive routine follow-up.

However, there were five case series which reported the proportion of relapsing patients who were identified as a relapse case during routine follow-up appointments and the number of cases who self-referred outside routine follow-up due to onset of symptoms or who were referred by their general practitioner (GP) or detected after an admission for another initial diagnosis. Two studies were conducted in the UK,{161},{162} two in the USA{163},{164} and one in India.{165}

Many of the studies found were performed 20 to 30 years ago, prior to the advent of modern treatment regimens. These studies generally concluded that routine follow-up was unnecessary, which may explain the dearth of studies on routine follow-up for previously treated TB patients since this time. In addition, the definition of relapse varied across studies and in all the studies (apart from one where it is not clear{164}) only patients with pulmonary TB were included.

8.1.3 Evidence statements

Detection by routine follow-up

In five case series studies of previously treated TB patients found to have relapsed, the percentage detected at routine follow-up clinic attendances were 27%,{165} 35%,{164} 40%,{163} 51%{161} and 58%{162} (one study{165} only included patients who had completed treatment). (**3**)

One study calculated that routine surveillance of 1,000 patients who had completed treatment would help to identify approximately six relapses in one year{165} whilst a yield of 0.6% of relapse cases detected from routine follow-up was calculated in another study.{164} (**3**)

Rate of relapse

In a UK study the relapse rate at five years since the start of treatment was 3.5%.{162} In another study 4% of patients with active TB added to a TB register over a 7.5-year period had been diagnosed with reactivated disease{163} whilst in

the Indian study the authors calculated a cumulative relapse rate of 11.6% at five years in patients who completed treatment.{165} (**3**)

Risk factors for relapse

Of the patients who relapsed in a UK study, 82% discharged themselves prematurely from hospital and/or terminated their own treatment.{162} In another study 75% of relapsed patients over a 7.5-year period had a combined treatment regimen which was self-interrupted or self-discontinued and a further 14% received no treatment or streptomycin only.{163} An Indian study{165} found the main reason for prolongation of treatment was irregular drug taking during the course of treatment. Patients who completed their course of treatment in less than 24 months had an overall relapse rate of 4.09 % in five years; those who required 24 to 30 months had a cumulative relapse rate of 10.85% ($p<0.05$). (**3**)

In a group of relapsed chronic sputum-positive patients, 57% had inadequate duration of treatment regimen (less than 18 months) and a further 23% had adequate duration but irregular treatment.{161} In another study 61% of relapsed patients were not treated for the recommended treatment duration of 18 months.{162} Of a group of relapsed patients detected during routine follow-up, 49% had inadequate treatment (<1 year) with an effective regimen, or interruption of treatment serious enough to make the possibility of at least one year of continuous treatment unlikely.{164} Of these relapsed patients, 94% were found to have 'complicating factors' which included inadequate therapy, alcoholism or poor cooperation. (**3**)

In one study{162} the relapse rate in men was nearly twice that in women and was also higher in patients over 45 years. The relapse rate did not seem to be related to the extent of the disease. In another study of treatment completion patients the cumulative five-year relapse rate did not differ significantly between men and women or in terms of age or extent of initial disease, initial cavitary status or presence of drug-resistant bacilli.{165} (**3**)

The mean time between last positive sputum smear and relapse in patients treated after 1955 (when adequate therapy was employed) was 7.5±4.88 years.{161} (**3**)

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8.1.4 From evidence to recommendations

All patients should receive 'inform and advise' information upon treatment completion. They should then inform other healthcare professionals, who may provide or organise their care in the future, of their history of latent TB or disease.

Routine follow-up was felt to be necessary for MDR TB, and worth considering for isoniazid-resistant TB, because these patients have received non-standard treatment with a potentially higher relapse rate.

The GDG felt that regular follow-up clinic visits were unnecessary. Patients should be advised to be alert to symptoms and to contact the TB service rapidly.

8.1.5 RECOMMENDATIONS

R59 Follow-up clinic visits should not be conducted routinely after treatment completion. D

R60 Patients should be told to watch for symptoms of relapse and how to contact the TB service rapidly through primary care or a TB clinic. Key workers should ensure that patients at increased risk of relapse are particularly well informed about symptoms. D(GPP)

R61 Patients who have had drug-resistant TB should be considered for follow-up for 12 months after completing treatment. Patients who have had MDR TB should be considered for prolonged follow-up. D(GPP)

Cross-referring:
For examples of 'inform and advise' information, see Appendix H.

8.2 Improving adherence: directly observed therapy

8.2.1 Clinical introduction

People with TB can either be given treatment to take without supervision (self-administered therapy) or under direct observation by a health professional or other person such as a family member, where the swallowing of the medication is observed. The latter is known as directly observed therapy. Intermittent (less often than daily) dosing regimens lend themselves to DOT because of the lower

frequency of dosing to supervise. The monitoring of DOT is however only one part of the WHO DOT strategy,{166} which has five elements.

1. Supervised medication taking.
2. Drug availability including reserve drugs.
3. Sputum testing facilities with quality control.
4. Patient tracking systems.
5. Political commitment at Governmental level.

The WHO advocates universal DOT as part of their overall strategy, the aim being to increase treatment completion rates to over 85%, which particularly for smear-positive pulmonary disease, is the level above which modelling shows that case numbers then begin to decrease. Treatment completion rates of over 90% however have been reported from both the USA and UK using mainly self-administered therapy and only selective – not universal – DOT.{160},{167}

Sceptics who have labelled DOT as 'supervised pill swallowing'{168} say that the success of DOT programmes is derived from the substantial technical and financial investment in tuberculosis programmes that the DOT strategy represents and not the DOT element itself.{169}

DOT is commonly used in the UK, as the 1998 BTS guidelines{68} recommended, for patients who are unlikely to comply, those with serious mental illness, patients with multiple drug resistances, and for those with a history of non-adherence with anti-tuberculosis medications, either in the past or documented during treatment monitoring. For those without multiple drug resistances, a three-times weekly regimen was recommended.

8.2.2 Current practice

Of the TB service providers participating in the review of current services, 79% in London and 80% elsewhere used DOT. Some of the other respondents stated that it was not needed. There was no obvious variation in the provision of DOT by notifications, personnel or specialist personnel, nor was there any correlation

between the number of patients given DOT and the number of notifications, personnel or specialist personnel. It would seem that the variation in practice is due to different clinical habits. Given the cost of DOT, it would seem timely to promote a consistent and evidence-based approach to its provision.

8.2.3 Methodological introduction

Three systematic reviews{170–172} and four additional RCTs{173–176} were identified comparing DOT with self-administered treatment. Two systematic reviews{171},{177} and one RCT{175} were excluded due to methodological limitations. The included studies were a Cochrane systematic review of six RCTs (four studies of patients being treated for active TB conducted in Thailand,{178} Pakistan{179} and South Africa{180},{181} and two US studies of individuals receiving preventive therapy for latent TB{182},{183}) plus a US study of homeless patients{176} and a study of illegal immigrants in Italy{174} both with latent TB on prophylaxis, and a study of active TB patients in Australia.{173}

Numerous elements of a DOT programme may affect cure and treatment completion rates and therefore it is difficult to isolate the contribution of observing the patient taking their TB medication. For example, the relationship a patient has with their observer or the distance of the clinic from a patient's home are integral parts of a DOT programme which may influence outcomes. This also means that due to the number of elements which may differ within a DOT programme and cultural differences between populations, it is difficult to generalise from one setting to another. The way it is possible to offer DOT services will be dependent on the way healthcare systems are configured and the resources available. DOT services may differ in terms of:

- hospital or clinic versus home-based DOT
- observers may be lay persons (community or family members who may or may not have received training or advice on DOT) or healthcare professionals (doctors, nurses or health visitors)
- DOT may be given throughout treatment or for only part of it
- DOT may be introduced with other (less explicit) elements which may affect outcomes, for example new enthusiastic staff, education, incentives (food, drink, travel vouchers etc), counselling or psychosocial support.

None of the studies identified were performed in the UK.

In terms of who should observe DOT, six RCTs comparing different types of DOT observers were identified. The studies were performed in Tanzania,{184},{185} Pakistan,{179} the USA,{176} Swaziland{186} and South Africa.{181}

A number of different types of observers are used in the studies and may not necessarily be comparable across studies. These were:

- a volunteering community member selected by a village leader who was interviewed and trained by a health worker, compared with observation by a health worker in the nearest health centre{185}
- a trained guardian (family member) or former TB patient compared to a health worker in a health facility{184}
- a health worker at a health facility where a patient met access criteria to the facility, compared with supervision by a family member who was orientated in the role{179}
- a lay health worker in the lay health worker's home compared with observation by a nurse at a clinic{181}
- a trained family member compared with a community health worker{186}
- a research assistant observing homeless patients at a study site with a $5 incentive compared with observation by a trained, paid, homeless peer health advisor.{176}

In the US study,{176} the monetary incentive in the research assistant observer arm meant that the contribution of the observer to this result was unclear.

Additional factors for consideration include the duration of supervision (this was only for the first two months in the studies in Tanzania{184},{185}), variable motivation and training of observers and the convenience of the site of the observation. None of the studies were UK based.

With regard to terminology in this area, in recent years use of the term compliance has been discouraged due to its connotations of patient subservience. The term adherence has instead been used to describe the patient's choice as to whether to complete treatment. More recently the term concordance has been recommended

to reflect 'the active exchange of information, negotiation, and spirit of cooperation'.{187}

8.2.4 Evidence statements

Efficacy of DOT

A Cochrane systematic review{172} found that patients allocated to DOT compared to self-administered treatment had similar outcomes in relation to cure and cure plus treatment completion based on a meta-analysis of four RCTs of patients with tuberculous disease.{178–181} In terms of population groups where DOT may be effective, only one of these RCTs (in sputum positive TB patients over 15 years of age with no previous treatment history for TB{178}) significantly favoured DOT (in terms of both cure (RR 1.13, 95%CI 1.04 to 1.24) and cure plus treatment completion (RR 1.11, 95%CI 1.03 to 1.18) compared with self-administered treatment. However, this study allowed participants to choose their supervisor and involved home visits by health workers every two weeks. (**1++**)

In an RCT of homeless patients in the USA{176} on prophylaxis for latent TB, no significant difference was found in treatment completion between a peer health advisor performing DOT and usual care (self-administered treatment). Treatment completion in a monetary incentive arm however (where DOT was provided by a trained research assistant and patients were given a monetary incentive at each visit), was significantly better than in the usual care arm (p=0.04). Residence in a hotel or other stable housing at entry into the study *vs.* residence on the street or in a shelter at entry was an independent predictor of treatment completion (OR 2.33, 95%CI 1.00 to 5.47). (**1++**)

In illegal immigrants on prophylaxis for latent TB{174} in Italy, those on supervised (directly observed clinic-based) treatment were significantly less likely to complete treatment than did those on an unsupervised regimen (p=0.006, log rank test). Treatment completion rates were 7.3% in the supervised group and 26% in the unsupervised group. (**1++**)

In an Australian RCT,{173} when comparing a family based programme of DOT for active TB patients with standard supervised but non-observed therapy no significant difference was found in relation to treatment completion or non-adherence. (**1+**)

Observers for DOT

None of three strategies tested in patients with active TB in Pakistan{179} (self-supervision, health worker DOT and family member DOTS) was superior to the others in terms of cure rate or cure rate and treatment completion combined. (**1++**)

In homeless patients in the US{176} on prophylaxis for latent TB, completion in the research assistant observer with monetary incentive arm was significantly better than in the peer health advisor arm (44% *vs*. 19%, p=0.01). (**1++**)

In patients treated for active TB in Tanzania,{185} no significant difference in biological conversion rate at two months or cure at seven months was found between institutional-based directly observed treatment and community-based directly observed treatment. (**1+**)

The cure rate and the treatment success rate (cure and treatment completion) for smear-positive patients in Tanzania{184} was not significantly different under community DOT (by a family member or former TB patient) compared with health facility-based DOT. (**1+**)

In new smear-positive patients in Swaziland,{186} there was no significant difference in cure rate or cure and completion rate between community health workers' and family members' DOT. (**1+**)

Treatment outcomes (cure combined with treatment completion) in South African{181} patients with active TB were not significantly different in the lay health worker supervision group compared to clinic DOT. (**1+**)

8.2.5 From evidence to recommendations

The generalised application of DOT is shown to be effective in only one study,{178} which allowed participants to choose their supervisor and also involved home visits by health workers every two weeks. One study in homeless men (street- or shelter-dwelling) in the USA indicated that, for street homeless men, financial incentives with personal support and/or more secure accommodation is associated with higher completion rates of treatment of latent TB infection when given as DOT. Studies in Australia and Italy did not show improved outcomes for those in the DOT arms. There is no high-level UK evidence in this area.

The interventions involved in DOT are not just supervised taking of medicines, but include increased contact and support. Given the resources required for DOT, and the attendant opportunity costs, the GDG decided not to recommend DOT for the general TB population. Improved adherence in both DOT and routine care may be achieved through more frequent contact with healthcare professionals.

Contamination between treatment arms in any DOT trial may have caused underestimated efficacy. In order to provide DOT, the infrastructure and culture of TB services changes (in particular, the emphasis given to ensuring treatment is completed). These changes may also have affected the control arms of studies. No trials have yet been conducted using designs to eliminate this effect.

There are also concerns about the outcomes which are necessarily used in these trials. Treatment completion and/or microscopy conversion are the outcomes used in trials to date, but the outcomes DOT aims to prevent are development of drug resistance and relapse of disease. Existing trials have neither the necessary long-term follow-up, nor are powered to look directly at these outcomes.

The model of DOT administered is also not optimum in most RCTs, for example if patients are sometimes expected to travel large distances for their treatment rather than DOT being available at the most convenient location. The only trial that allowed patients to have an input into where DOT was administered did find a beneficial effect. This is an issue of applicability for trials conducted in developing countries.

The GDG could not reach unanimity on making a recommendation to limit the use of DOT, but agreed that it is not useful in the UK as a universal mode of TB treatment, and consequently set out to recommend groups in whom DOT may be useful, and for whom it should be considered on an individual basis.

The GDG felt that evidence was sufficient to require a recommendation on DOT for street- or shelter-dwelling homeless people. The GDG did not feel able to make a recommendation to use DOT routinely for people with histories of alcoholism, drug abuse or mental illness.

One of the studies considered{176} indicates some effect of stable housing on adherence. Considering this and the multifaceted support contained within DOT programmes, the GDG regarded it as crucial to DOT's success that environmental and psychosocial factors, and the pragmatic patient-centred delivery of DOT, be considered at the start of the patient's treatment.

2006

8.2.6 RECOMMENDATIONS

R62 Use of DOT is not usually necessary in the management of most cases of active TB. A All patients should have a risk assessment for adherence to treatment, and DOT should be considered for patients who have adverse factors on their risk assessment, in particular:

- street- or shelter-dwelling homeless people with active TB B
- patients with likely poor adherence, in particular those who have a history of non-adherence. D(GPP)

R63 Clinicians who are planning to offer a course of DOT should consider ways to mitigate the environmental, financial and psychosocial factors that may reduce adherence, including stability of accommodation, prescription charges and transport. The setting, observer and frequency of treatment should be arranged to be most practicable for the person with TB. The person with TB and his or her assigned key worker should be involved in deciding these arrangements. DOT should also be supported by frequent contact with the key worker (see 8.3). D(GPP)

2006, amended 2011

8.3 Improving adherence: non-pharmacological strategies

2006

8.3.1 Clinical introduction

With regard to terminology in this area, in recent years use of the term compliance has been discouraged due to its connotations of patient subservience. The term adherence has instead been used to describe the patient's choice as to whether to complete treatment. More recently the term concordance has been recommended to reflect 'the active exchange of information, negotiation, and spirit of cooperation'.{187}

Concordance on TB treatment has been recognised as an issue for many years.{188} Problems can arise with both physicians' adherence with recommended

regimens and with patients' adherence with the agreed treatment.{189},{190} Adherence is the single most important determinant of treatment outcome, with poor adherence being strongly associated with treatment failure and relapse.{72} Strategies to improve adherence with treatment are therefore very important in those patients taking self-administered treatment. Any measure which increases adherence is therefore likely to improve outcome, by increasing the cure and completion rate, and reducing the failure rate of treatment and the relapse rate after treatment completion.

8.3.2 Current practice

Improving adherence

Participants in the review of current services were asked about incentives and measures to improve adherence to therapy, including free prescriptions.

94% of clinics in London, and 73% of participants outside London, reported using some measures to improve adherence. Most clinics reported using urine assays, examining urine colour, using tablet counts, and controlled dosage systems. Other respondents (outside London) also asked patients to sign care plans with regular support or gave the patients tablet diaries. Five responders outside London cited the use of home visits as a measure of improving adherence. There was no apparent variation by notifications, personnel or specialist personnel which might account for some clinics providing these while a few do not. As these simple measures appear to be almost universally used, and given the potential benefits, it seems appropriate that all clinics have some such measure available, unless their work is only in screening, vaccination or contact tracing.

61% of clinics in London, and 19% of participants outside London, used incentives to increase clinic attendance. Respondents mainly reported refunding travel costs, but others stated were food and prizes for children. Three clinics (all in London) offered cash. There was no obvious variation by notification rates in the clinics using incentives outside London, although there may be a trend in London toward high-notification clinics using incentives. This may explain the contrast in use between London and the rest of England and Wales. There was no obvious variation by personnel or specialist personnel.

Only 16% of participants outside London had free prescriptions. Within London, this figure was 67%. The contrast between London and elsewhere may be because within London, the use of free prescriptions appeared to be related to the clinics that had more nursing staff.

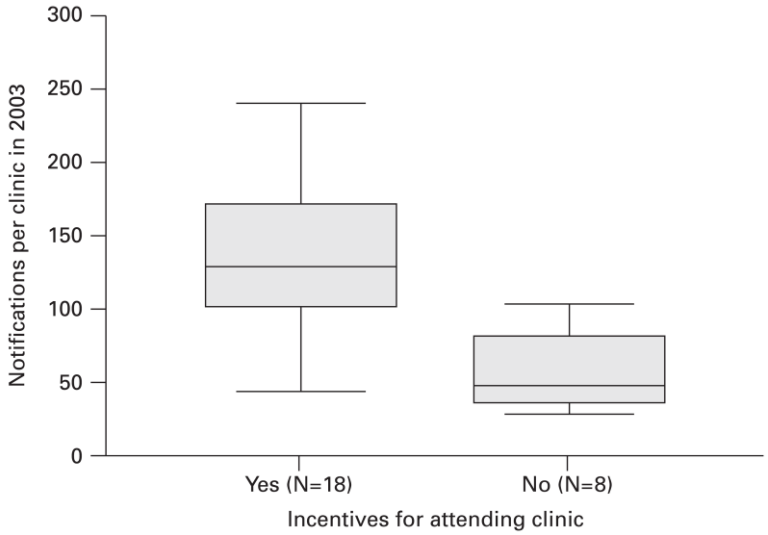

Figure 5 Box plot of notifications of TB per clinic in London, by use of incentives

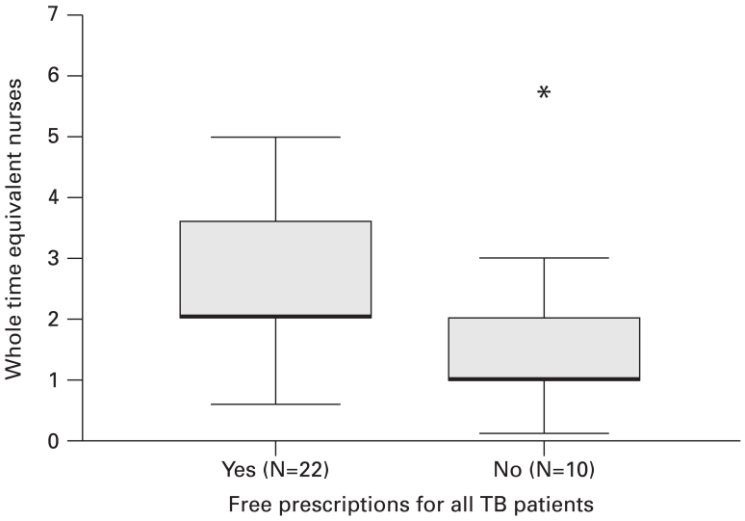

Figure 6 Box plot of notifications of TB per clinic in London, by use of free prescriptions

Outreach work

Some form of outreach was carried out by 67% of clinics outside London. Within London, this was 82%. Most outreach was to patients' homes. Some respondents reported outreach in care homes, detox shelters and other drug treatment venues,

homeless shelters, clubs and other community centres and places of work. Variation in the provision of outreach work was not obviously explained by caseload (notifications), staffing levels or availability of specialist personnel.

8.3.3 Methodological introduction: adherence among patients on treatment for active TB

A systematic review{191} examined the evidence from five randomised trials of the effectiveness of various strategies to promote adherence. The review included two trials of patients with active TB,{192},{193} two trials of those on prophylactic drug treatment for latent TB{194},{195} and one trial which included both groups.{196} As the review included trials of both patient groups and did not attempt statistically to combine the results, it was thought that it would be more informative to evaluate the trials on an individual basis.

In terms of strategies to promote adherence in those with active TB, a trial performed in India{193} compared outcomes in those defaulters who failed to collect their drugs and then did or did not receive reminder letters. Two studies included in the systematic review,{191} performed in Korea{192} and the USA{196} were excluded due to methodological limitations.

Three further RCTs were found. Another Indian study compared two policies of default management{197} while a trial performed in Pakistan{198} studied the impact of intensive counselling on treatment outcomes. A third RCT{199} was excluded due to methodological issues.

Two cohort studies and a case control study were also identified. A cohort study performed in South Africa{200} assessed whether the combined strategy of a patient-centred interview plus the issuing of a patient education booklet would increase adherence to treatment. The other cohort study{201} was excluded due to methodological limitations as was the case control study.{202}

Strategies to promote adherence may be specific to their setting, population or treatment (in terms of drug, dose and duration) and thus not generalisable. No studies were identified which had been performed in UK populations.

8.3.4 Methodological introduction: adherence among patients on prophylactic drug treatment for latent TB

With regard to strategies to promote adherence in those with latent TB, the systematic review{191} on adherence strategies for TB treatment included two trials of those on prophylactic drug treatment for latent TB.{194},{195}

One of these studies in a homeless population{194} was excluded on the basis that the only outcome measure was adherence to first referral. The other study{195} however was excluded on the basis of methodological limitations.

Five further studies were found that were not included in the systematic review.{191} One of these was excluded due to methodological limitations.{203}

Of the four remaining studies, all were American trials. Two studies{204},{205} were in adolescents (mainly of Latino origin). One{204} looked at the effects of adherence coaching, self-esteem counselling and usual care on treatment completion. In the other study{205} peer counselling, parent participant contingency contracts, both of these interventions combined and usual care interventions were assessed. Another study{206} was in prisoners released whilst on TB prophylaxis who received either education or the promise of an incentive (a food or travel voucher) when attending the TB clinic. The final study was in a community-based population of homeless adults who received either a cash or non-cash incentive of equivalent value when attending their TB clinic appointments.{207}

Few high-quality trials have been completed, and where there are studies, these are in very specific non-UK population groups raising generalisability concerns. Furthermore, in these studies it is often difficult to assess the contribution of increased attention and motivation from healthcare professionals or other individuals, rather than an intervention itself, which may have been responsible for improved outcomes.

8.3.5 Evidence statements

Active disease

In a study conducted in India{193} a significantly higher treatment completion rate (88%) was achieved among a group of patients who received reminder letters when

they defaulted (failed to collect their TB medication) in comparison to patients in a group where no action was taken for default (73%) ($p<0.001$). (**1+**)

The default rate of the intervention group in a Pakistani study{198} who received monthly health education counselling was 46.6% which was significantly lower compared to 53.6% in the control group (RR 0.87, 95%CI 0.77 to 0.98, $p=0.03$). (**1+**)

Two policies of default management were compared in an Indian study.{197} Under routine policy, failure to collect TB drugs within three days resulted in a reminder letter and then a home visit on the 11th day and then no further action, whilst under the intensive policy, home visits were made on the same day and followed by further visits at one and two months. No statistically significant difference was found. (**1+**)

In a study conducted in South Africa,{200} the relative risk of being non-adherent to treatment at the control clinic (standard clinic treatment) compared to the intervention clinic (where patients received a patient-centred interview and a health education booklet in addition to standard clinic treatment) was 4.3 (95%CI 1.3 to 14.5, $p=0.014$). (**2+**)

Latent infection

In teenage people of Latino origin in the USA on treatment for latent TB,{204} the coaching condition (where bilingual Latino college students were trained to provide education concerning latent TB and treatment) had the highest cumulative mean number of pills consumed over six months (129.27), and members of the coaching group took significantly ($p<0.05$) more pills than members of the usual care (113.09) and self-esteem groups (112.02) (in the latter bilingual Latino college students served as self-esteem counsellors). Treatment completion however, was not significantly different between the three groups. (**1+**)

In a study performed in the USA of adolescents on treatment for latent TB,{205} treatment completion rates did not vary significantly across study groups. Treatment was completed by 84.8% of participants in the combined intervention group (peer counselling and incentives), 80.3% in the peer counselling group (adolescents who had completed therapy for latent TB were recruited and trained as peer

counsellors), 77.8% receiving usual care (treatment and educational services customarily provided by the clinic) and 76.4% in the incentive group (parents and adolescents negotiated an incentive provided by the parent to be received if the adolescent adhered to the prescribed TB treatment). (**1+**)

In US prisoners released whilst on treatment for latent TB,{208} rates of completion of therapy were 23% in the education group (where patients were seen every two weeks for the duration of their stay, to reinforce initial information), 12% in the incentive group (patients were able to choose food or transport vouchers of equivalent cash value if they went to the TB clinic within one month of release) and 12% in the control group (where there was no further contact with study personnel). Those in the education group were more than twice as likely as those in the control group to complete treatment (adjusted OR 2.2, 95%CI 1.04 to 4.72, p=0.04), whereas treatment completion in the incentive group did not significantly differ from the controls. (**1+**)

In a community-based population of homeless adults in the USA on TB prophylaxis,{207} no statistically significant difference in completion was found between those in a cash arm (89%) who received a monetary incentive for keeping each twice-weekly medication appointment and those in the non-cash incentive arm (81%), who could choose fast-food or grocery store coupons, telephone cards or bus tokens with an equivalent face value. (**1++**)

8.3.6 From evidence to recommendations

It is important to involve the patient in treatment decisions, and emphasise the importance of adherence through education in an appropriate language.

In the GDG's experience, useful adherence strategies include:

- reminder letters in appropriate languages
- supervision and support from healthcare workers
- home visits
- patient diaries
- urine tests and other monitoring (for example, pill counts) during visits by a nurse or health visitor

- an appropriately trained and experienced named key worker
- assisting or advising patients regarding links to social security benefits and housing/social services.

Involvement of primary care professionals throughout a course of anti-tuberculosis drugs may also promote adherence.

Prescriptions for people with TB are not free in all parts of England and Wales. This clearly complicates the work of clinicians trying to improve adherence to therapy. The Chief Medical Officer's TB Action Plan{2} sets as one of its essential actions to improve TB services 'explore ways of reducing the cost of TB drugs to patients, and of facilitating their dispensing'. The GDG considered this issue but it is not the role of NICE guidelines to address charges for NHS services at the point of delivery, and no recommendation has been made.

It is important to ensure the availability of liquid drug preparations, to assist treatment of children or people who have swallowing difficulties. However, it should be noted that pharmacies may need up to a week to access these medicines in liquid form and therefore there is a need to ensure prescriptions are written in advance of the patient's current supply running out. If a community pharmacist is involved in the supply of these drugs then discharge summaries/clinic letters and prescriptions will need to be provided to the community pharmacist at the earliest opportunity to ensure a continuous supply.

The GDG considered the difference demonstrated in default rate in one of the studies,{198} while statistically significant, to be small and clinically insignificant. Another study{208} had shown a significant difference in completion rates but both groups had rates that would be very poor in a UK context.

Recommendations are also given here to assist adherence through patient and public information (see chapter 4 for further details). Patient and public information is available in many languages.

8.3.7 RECOMMENDATIONS

R64 To promote adherence, patients should be involved in treatment decisions at the outset of treatment for active or latent TB. The importance of adherence should

be emphasised during discussion with the patient when agreeing the regimen. D(GPP)

R65 The TB service should tell each person with TB who their named key worker is, and how to contact them. This key worker should facilitate education and involvement of the person with TB in achieving adherence. D(GPP)

R66 TB services should consider the following interventions to improve adherence to treatment for active or latent TB if a patient defaults:

- reminder letters in appropriate languages B
- health education counselling B
- patient-centred interview and health education booklet B
- home visits D(GPP)
- patient diary D(GPP)
- random urine tests and other monitoring (for example, pill counts) D(GPP)
- information about help with paying for prescriptions D(GPP)
- help or advice about where and how to get social security benefits, housing and social services. D(GPP)

R67 Pharmacies should make liquid preparations of anti-TB drugs readily available to TB patients who may need them – for example children and people with swallowing difficulties. D(GPP)

R68 TB services should assess local language and other communication needs and, if there is a demonstrated need, provide patient information accordingly.[11] D(GPP)

2006

[11] Patient information should be drawn from national high-quality resources if available; for examples, see www.hpa.org.uk or www.nks.nhs.uk

9 Risk assessment and infection control in drug-resistant TB

9.1 Risk factors

9.1.1 Clinical introduction

Drug resistance is an important issue in the management of TB, as it may prolong the period during which patients are infectious to others as well as compromising the effectiveness of treatment. Resistance to particular single drugs develops in individual bacteria by natural mutations in between one in 10^5 and one in 10^7 organisms, depending upon the drug in question. Multiple drug combinations overcome this problem provided enough drugs are given and taken correctly, but modification of the treatment may be required. Resistance to TB drugs is defined as a level of resistance to four times or greater the concentration of drug required to inhibit a fully susceptible organism.

Resistance can be acquired, in a patient with a fully susceptible organism, by inadequate drug treatment being prescribed (physician error) and/or inadequate adherence with treatment (patient error). Resistance can be also be primary, with a patient being infected with an already drug-resistant organism, thus having drug resistance without a prior treatment history. Resistance can be to a single drug, for example mono-resistance to isoniazid, or to multiple drugs, for example to both isoniazid and streptomycin. MDR TB is defined as high-level resistance to both rifampicin and isoniazid with or without additional drug resistances.

Controlled clinical trials for respiratory tuberculosis show that 100% of cases positive on microscopy and culture pre-treatment have become negative on culture after four months of standard treatment.{209} Positive cultures after four months treatment, ie in month five or later, therefore by definition represent treatment failure.{210} Cases of treatment failure have a high chance of having developed acquired drug resistance, which can be rapidly assessed with molecular probes for rifampicin resistance and a repeat drug susceptibility profile.

MDR TB is important because there is loss of both the main bactericidal drug (isoniazid) and the main sterilising drug (rifampicin). The consequences of this

situation are considerable. Such patients who are sputum smear positive remain infectious for much longer than those with susceptible organisms, have a higher death rate from, and a lower cure rate for, their tuberculosis, require individualised complex regimens using multiple reserve drugs of higher toxicity, and cost at least £50,000–70,000 each to treat.{211}

Drug resistance in TB is found in nearly all settings in the world, but some countries or areas have higher levels of drug resistance and MDR TB than others. Drug resistance in England, Northern Ireland and Wales has been monitored continuously by MycobNet, based at the Centre for Infections, Colindale (see chapter 14 for details). This information is available at www.hpa.org.uk

International monitoring of drug resistance is undertaken by the WHO and IUATLD.{212} Russia and the Baltic states recently joining the European Union (Estonia, Latvia and Lithuania) have had high levels of MDR TB (>5% of all cases) reported, as have Argentina, Côte D'Ivoire, Dominican Republic, Iran, and some parts of China and India.

9.1.2 Methodological introduction

Studies were sought that examined risk factors for any type of drug resistance or MDR TB. However, if the study population was dissimilar to the UK the studies were excluded. Thus studies from most developing countries were excluded except those in sub-Saharan Africa and India or Pakistan, as these represent significant ethnic minority groups in the UK. Other studies from Japan, Taiwan, or localised areas of the USA and European countries were excluded as these were felt not to be representative of the ethnic mix of the UK population. National studies undertaken in European countries were included.

Thirteen studies were identified which met the above criteria. Four of these studies were analyses of drug resistant TB in the UK,{213–216} four studies were performed in sub-Saharan Africa,{215},{217–220} and additionally there were studies undertaken in the USA,{221} France,{222} The Netherlands,{223} Switzerland{224} and India.{225} Two studies (one in sub-Saharan Africa and one in India) were excluded due to methodological limitations.{217},{225}

Most studies reported national surveillance data and were graded as level 2 as they involved significant comparative analysis even if they did not fall strictly into a case control study design type. It should be noted that the UK studies which cover notified TB cases over the same time period will include the same cases in their analyses.

The retrospective nature of these studies often means data about some risk factors is not recorded in detail or at all, so there may be incomplete risk factor data. This is especially true of HIV status, which for many patients is often unknown.

To aid comparison, the number of participants included in each study is indicated.

9.1.3 Evidence statements

All evidence statements are graded level 2+.

Table 30: Risk factors

Study	Association
Age as a risk factor	
UK national surveillance study{213} (N=25,217)	A slightly higher proportion of isoniazid resistance (7.6%) was observed in those aged 15–44 years than in other age groups. This was significantly higher than in those aged >44 years for isoniazid resistance only and significantly higher than in those aged >65 years for MDR TB.
UK study based in one London hospital{214} (N=121)	Patients with drug-resistant TB were younger than those with drug-sensitive TB (OR 1.03, 95%CI 1.02 to 1.05, p<0.001). The mean age of those with resistance to more than one first-line drug was 40 years, resistance to only one first-line drug was 32 years and drug-sensitive TB was 47.4 years.
National US study{221} (N=67,340)	Those who were younger than 65 years were at increased risk of drug resistance to at least isoniazid with adjusted OR 1.7 (95%CI 1.4 to 2.2) for those aged 0–14 years, 2.0 (95%CI 1.8 to 2.2) for those aged 15–24 years, 1.8 (95%CI 1.6 to 1.9) for ages 25–44 years and 1.4 (95%CI 1.3 to 1.6) for those aged 45 to 64 years.
National surveillance study in Switzerland{224} (N=1,056)	An increased risk of resistance to any first-line drug was associated with being <65 years of age (adjusted OR 1.5, 95%CI 1.0 to 2.3).
National surveillance study in the Netherlands{223} (N=1,836), a surveillance study in Kenya{218}	No significant association was found between age and drug resistance.

(N=491) and two South African studies{219},{220} (N=7,266 and N=275 respectively)	
Prior treatment history as a risk factor	
UK national surveillance study{213} (N=25,217)	Those reported to have had a previous episode of TB, exhibited a significantly higher proportion of resistance to at least isoniazid (15.5%) and MDR (9.4%) than either those patients who had never had TB (5.7% and 0.8% respectively), or those whose history regarding previous TB was not available (4.9% and 0.7%, respectively; p<0.001 (isoniazid resistance); p<0.001 (MDR)).
UK study of TB patients in England and Wales reported during two time periods (1993 to 1994 and 1998 to 2000){216} (N=9,541)	There was a strong association between previous treatment and MDR TB (OR 9.1, 95%CI 6.3 to 13.2). This overall relationship was weaker for isoniazid resistance (OR 1.6, 95%CI 1.2 to 2.1).
UK study based in one London hospital{214} (N=121)	The highest risk for resistance to any drug was associated with previous treatment for TB (OR 22.85, 95%CI 5.1 to 102.5; p<0.001).
UK study in Leicestershire{215} (N=104)	Previous history of TB (OR 3.7, 95%CI 1.2 to 11.8, p=0.022) was significantly associated with resistance to at least one first line drug.
National US study{221} (N=67,340)	For resistance to any drugs and the combination of isoniazid and rifampin (MDR TB), the rate of resistance was higher among patients with prior TB compared with those without prior TB (p<0.05). Those with prior TB were at increased risk of resistance to at least isoniazid with an adjusted OR of 2.6 (95%CI 2.4 to 2.9).
French national surveillance study{222} (N=2,998)	An increased risk of resistance to any drug (OR 2.7, 95%CI 2.0 to 3.8) and MDR TB (OR 10.2, 95%CI 4.1 to 25.3) was associated with previous history of treatment. Similarly, unknown treatment history was associated with an increased risk of resistance to any drug (OR 1.7, 95%CI 1.2 to 2.5) and MDR TB (OR 3.4, 95%CI 1.1 to 11.2).
National surveillance study in the Netherlands{223} (N=1,836)	Rates of acquired resistance (those who had been previously treated for TB) to isoniazid alone (11.4%) and isoniazid and rifampicin (MDR TB, 5.7%) were higher than rates of primary resistance (those who had never been diagnosed with TB before) to these drugs (5.2% and 0.7% respectively, p<0.05)
National surveillance study in Switzerland{224} (N=1,056)	An increased risk of resistance to any first-line drug was associated with previous history of treatment (adjusted OR 7.3, 95%CI 3.9 to 13.6).
Surveillance study of 26 districts in Kenya{218} (N=491)	Of 90.6% of patients with no history of previous treatment, 6.3% had a resistant strain while of 9.4% with a previous history of anti-

2006

	tuberculosis drug treatment, 37% had a resistant strain (p<0.005).
South African study analysing rates of drug resistance in the West Cape region{219} (N=7,266)	Patients with a history of TB treatment were found to be at an increased risk of developing drug resistance (RR 2.6).
South African study based in one hospital{220} (N=275)	No significant association was found between previous treatment history and drug resistance.
Previous TB status in addition to other risk factors	
In a UK study of TB patients reported during two time periods (1993 to 1994 and 1998 to 2000){216} (N=9,541)	In those with previous TB, significant risk factors for isoniazid resistance were smear positive status (OR 3.2, 95%CI 1.1 to 9.2) and being of non-UK origin but arriving in the UK in the past 10 years (OR 3.2, 95%CI 1.4 to 7.0). This was similar for MDR TB where the most significant risk factors were smear positive disease (OR 5.9, 95%CI 1.8 to 19.0) and non-UK origin – particularly those who had arrived in the last five years in whom the risk compared with UK-born was approximately sixfold (OR=0.58, 95%CI 1.8 to 18.5). In those without previous TB, significant risk factors for isoniazid resistance were London residence (OR 1.4, 95%CI 1.1 to 1.7), being HIV positive (OR 2.4, 95%CI 1.1 to 5.2) although this was only significant in 1993 to 1994 (OR 2.4, 95%CI 1.1 to 5.2), and ethnicity. Compared with the white ethnic group, adjusted odds ratios were similar in people of Indian (subcontinent) origin (OR 1.6, 95%CI 1.2 to 2.1), people of black African origin (OR 1.7, 95%CI 1.2 to 2.4) and other ethnic groups combined (OR 1.9, 95%CI 1.3 to 2.8). For MDR TB the most significant risk factors were being HIV positive (OR 2.5, 95%CI 1.2 to 5.2) and London residence (OR 2.0, 95%CI 1.2 to 3.3). Birth outside the UK was also important, with the risk of MDR TB higher for those arriving in the last five years (OR 3.2, 95%CI 1.4 to 7.3).
Ethnicity as a risk factor	
UK national surveillance study{213} (N=25,217)	Among the three ethnic groups from whom substantial numbers of isolates were received, the highest proportion of resistance to at least isoniazid and MDR TB was reported in isolates from people of black African origin (10.1% and 2.0% respectively) with 7.2% and 1.4% in those originating from the Indian subcontinent, and 4.1% and 1.4% in those of white ethnic origin. Resistance to at least isoniazid was significantly different between all three ethnic groups (p<0.001).
UK study based in one London hospital{214} (N=7,266), Kenyan study{218} (N=491), South African study{219} (N=7,266)	No significant association was found between Caucasian and non-Caucasian ethnicity and drug resistance{214} and in the other two studies similarly no association was found

2006

	between drug resistance and ethnic group.	
Gender as a risk factor		
UK national surveillance study{213} (N=25,217)	The proportion of those resistant to at least isoniazid was higher in men (5.9%) than in women (5.4%), although the difference was not significant. However, men were significantly more likely to have MDR TB (1.4% *vs*. 0.9%, p<0.001).	
National surveillance study in Switzerland{224} (N=1,056)	Increased risk of resistance to any first-line drug was associated with male sex (adjusted OR 1.4, 95%CI 1.1 to 2.0).	
UK study based in one London hospital{214} (N=121), national surveillance study in the Netherlands{223} (N=1,836), Kenyan study{218} (N=419), two South African studies{219},{220} (N=7,266 and N=275 respectively)	No association was found between drug resistance and gender.	
Place of birth as a risk factor		
UK national surveillance study{213} (N=25,217)	People born outside the UK were significantly more likely to have resistance to at least isoniazid than those born in the UK (9.1% *vs*. 4.2%, OR 2.27, p<0.001). Similarly, 2.0% of people born outside the UK had an MDR isolate compared with 1.0% of those born in the UK (OR 1.97, p<0.001).	
National US study{221} (N=67,340)	Foreign-born cases had significantly higher rates of resistance to isoniazid (12.4% *vs*. 6.4%, p<0.05) and streptomycin (10.0% *vs*. 4.3%, p<0.05) than US-born case patients but similar rates of rifampin resistance (3.1% *vs*. 2.9%) and MDR TB (2.4% *vs*. 2.0%). Those who were foreign born were at increased risk of resistance to at least isoniazid with an adjusted OR 1.5, 95%CI 1.4 to 1.6.	**2006**
French national surveillance study{222} (N=2,998)	An increased risk of resistance to any drug (OR 1.7, 95%CI 1.3 to 2.2) and MDR TB (OR 2.7, 95%CI 1.1 to 6.2) was associated with foreign birth.	
National surveillance study in the Netherlands{223} (N=1,836)	Drug resistance was reported in 9% of patients born in the Netherlands and in 18% of foreign-born TB patients (p<0.001).	
National surveillance study in Switzerland{224} (N=1,056)	Foreign-born patients showed a slightly but not significantly elevated risk of resistance (adjusted OR 1.5, 95%CI 0.8 to 2.8).	
Two UK studies, (N=121){214} (N=104){215} and a Kenyan study {218} (N=491)	Drug resistance was not associated with foreign birth.	
Place of diagnosis as a risk factor		
UK national surveillance study{213} (N=25,217)	Compared with other English NHS regions and Scotland, Northern Ireland and Wales, patients diagnosed in London were more likely to have isolates resistant to at least isoniazid (7.6% *vs*. 4.6%, p<0.001). Similarly, patients from	

	London were more likely to have MDR isolates (1.7% *vs*. 0.9%, p<0.0001).
HIV status as a risk factor	
UK national surveillance study{213} (N=25,217)	Those known to be co-infected with HIV were more likely to be either resistant to at least isoniazid (11.6% *vs*. 5.5%) or be MDR (4.6% *vs*. 1.1%) than those from people of unknown or negative HIV infection status (p<0.001 (isoniazid resistance); p=<0.001 (MDR)).
National US study{221} (N=67,340)	For all drugs, resistance was significantly higher (p<0.05) in HIV-positive *vs.* HIV-negative patients and HIV-positive *vs*. those with unknown status, except for patients with isolates resistant to ethambutol. Those who were HIV positive were at increased risk of resistance to at least isoniazid with an adjusted OR 1.6 (95%CI 1.4 to 1.8).
French national surveillance study{222} (N=2,998)	An increased risk of resistance to any drug (OR 1.7, 95%CI 1.2 to 2.4) was associated with HIV positive status however an association was not found for MDR TB.
National surveillance study in the Netherlands{223} (N=1,836)	HIV positivity was more frequently reported in the drug-resistant group than in the drug-susceptible group (7.7% *vs*. 4.9%) but this difference was not significant.
South African study based in one hospital{220} (N=275)	No significant association was found between HIV status and drug resistance.
History of poor treatment adherence as a risk factor	
UK study in Leicestershire{215} (N=104)	Poor adherence (OR 4.8, 95%CI 1.4 to 14.4, p=0.005) was significantly associated with resistance to at least one first-line drug.
Other risk factors	
UK study based in one London hospital{214} (N=121)	Bilateral disease at presentation was associated with drug resistance (OR 8.5, 95%CI 2.1 to 35.0, p<0.005) but not with recent entry to the UK for foreign-born patients, alcoholism, psychological disturbances, homelessness, living in care homes or poor understanding of the English language (although for many of these risk factors patient numbers identified were very small).
UK study in Leicestershire{215} (N=104)	No significant associations were found between site of TB, foreign travel or recent immigration and resistance to at least one first-line drug (although it should be noted that only a small number of participants had these risk factors).
In a national surveillance study in the Netherlands{223} (N=1,836)	Asylum seekers diagnosed on arrival in the Netherlands showed an increased risk of resistance to any drug with 4.8% of cases in the drug-susceptible group and 10.4% in the drug-resistant group (p<0.001). With regard to site of disease and other clinical features (diabetes, malignancy and pregnancy) and a number of other risk groups (sailors, travellers,

2006

	illegal immigrants, the homeless, alcohol users, drug users, prisoners and healthcare workers), no differences were observed between the groups.

9.1.4 From evidence to recommendations

The GDG noted that the evidence base came from studies conducted in different parts of the world. The most significant risk factors depend on the population within which a drug-resistant strain is transmitted. Even factors found to be valid for London should not be extrapolated to the whole of England and Wales.

One of the UK studies{215} was noted to be a sub-population of the larger population-wide study.{213}

The data clearly show that there are a number of risk factors for drug resistance, which listed in order of importance for relative risk are as follows.

1. A history of prior TB drug treatment.
2. Birth in a foreign country, particularly sub-Saharan Africa and the Indian subcontinent.
3. HIV infection.
4. Residence in London.
5. Age profile, with highest rates between the ages of 25 and 44 years.
6. Male gender.

The GDG also regarded contact with a known case of TB, and treatment failure as risk factors.

It is still not known whether risk factors for MDR TB are the same as those for lesser forms of drug resistance.

Based on the conclusions of section 5.3, rifampicin-resistance molecular probes were recommended for those patients with risk factors.

The absence of risk factors is not enough in itself to remove clinical suspicion of drug-resistant TB.

The GDG agreed that intensive contact tracing should be carried out in all cases of MDR TB.

The GDG recognised the dangers associated with failure of drug treatment, and sought to advise readers that it needs to be recognised early.

9.1.5 RECOMMENDATIONS

R69 A risk assessment for drug resistance should be made for each patient with TB, based on the risk factors listed below: C

- History of prior TB drug treatment; prior TB treatment failure.
- Contact with a known case of drug-resistant TB.
- Birth in a foreign country, particularly high-incidence countries as defined by the HPA on its website.[12]
- HIV infection.
- Residence in London.
- Age profile, with highest rates between ages 25 and 44.
- Male gender.

R70 The TB service should consider the risk assessment for drug resistance and, if the risk is regarded as significant, urgent molecular tests for rifampicin resistance should be performed on smear-positive material or on positive cultures when they become available (see section 5.2). D(GPP)

R71 Response to treatment should be closely monitored in patients at increased risk of drug resistance. If there is no clinical improvement, or if cultures remain positive after the fourth month of treatment ('treatment failure'), drug resistance should be suspected and treatment reviewed with a clinician experienced in the treatment of MDR TB. D(GPP)

(See section 6.1 for details of the standard recommended regimen.)

2006

[12] Countries with more than 40 cases per 100,000 per year, as listed by the Health Protection Agency go to www.hpa.org.uk and search for 'WHO country data TB'.

9.2 Referral

9.2.1 Clinical introduction

MDR TB comprises some 0.8–0.9% of culture-confirmed TB cases in the UK, mainly in England and Wales.{140} As such they represent only 30–40 cases per year in number, but they have disproportionate importance because of:

- a prolonged infectious potential in pulmonary disease
- the need for higher levels of infection control, with negative pressure ventilated side wards, because of this and the potential adverse effects of acquiring the organism
- a much greater cost to treat, a minimum of £50–70,000 per case{211}
- prolonged treatment, often requiring multiple second-line drugs with an increased toxicity profile
- worse cure and survival rates, in both HIV-negative and HIV-positive individuals{226–230}
- the risk to healthcare workers and other contacts if they become infected.

Because treatment is complex, time consuming and demanding on both the patient and the physician, practice to date, based on BTS guidelines for treatment,{68} has been that treatment is only carried out:

- by physicians with substantial experience in drug-resistant TB
- in hospitals with appropriate isolation facilities (a negative pressure room)
- in close conjunction with the HPA and HPA regional centres for mycobacteriology.

Clinical management of these cases is not addressed by this guideline, as it is a rare, highly specialised and highly individualised activity, which may include second-line drugs, close monitoring, full supervision of treatment and surgical options. It is therefore the concern of this guideline to promote transfer of patients to an appropriate unit.

2006

9.2.2 Methodological introduction

A retrospective cohort study{231} performed in the USA was identified, which examined the treatment experience of patients diagnosed with MDR TB who were managed for at least part of their time on treatment in a specialist TB hospital. This study was excluded due to limitations in the methodology.

No studies of sufficient quality were found pertaining to whom (or where) MDR TB patients should be referred in order for them to achieve the most favourable treatment outcomes. Therefore, no evidence statements have been made in this section.

9.2.3 From evidence to recommendations

The GDG were aware that there are still relatively few cases of MDR TB in the UK each year, but noted that this represents a vitally important area in TB control and a unique challenge for treatment. The GDG felt that treatment failure (non-concordance) is a significant risk factor for drug resistance.

People with MDR TB are not always treated under the care of an MDR TB specialist. It was felt that there had been no evidence to support change in current practice in MDR TB referral since the BTS's code of practice.{6}

Patient acceptability and shared care arrangements need to be considered when arranging referral, and hence this section gives recommendations for discussing and consulting with specialist colleagues.

9.2.4 RECOMMENDATION

R72 The options for organising care for people with MDR TB should be discussed with clinicians who specialise in this. The views of the patient should be sought and taken into account, and shared care should be considered. D(GPP)

9.3 Infection control

9.3.1 Clinical introduction

Patients with sputum microscopy-positive MDR TB are no more infectious than similar patients with fully susceptible TB, ie they should not infect a higher proportion of contacts, because the organism is no more virulent. The

consequences of acquiring MDR TB infection and then disease, however, are much more serious than for fully susceptible TB, because MDR TB needs prolonged treatment (often with more toxic second-line drugs) and the outcome in terms of death and proportions cured are worse. Because of the loss of the most effective killing drug (isoniazid), and the most effective sterilising drug (rifampicin), such patients take much longer to become non-infectious than if organisms are fully susceptible (covered in section 6.5). In these cases there is not the rapid fall in numbers of viable organisms in the sputum seen in drug-susceptible cases, so they have a much prolonged infective potential after starting treatment.

Because of these differences it has been advised that patients with suspected or proven MDR TB should be isolated in a negative pressure room (as defined in recommendations below), and staff should wear FFP3 masks meeting the standards of the Health and Safety Executive{104} during patient contact whilst the patient is considered infectious.

The two major nosocomial outbreaks of MDR TB in the UK occurred because of failures in infection control procedures, either by carrying out risky procedures such as sputum induction in a communal HIV setting, or by isolating patients with active disease in a setting which had positive rather than negative pressure to the main ward.{232}

In 2005, the Chief Medical Officer's TB Action Plan{2} identified this as an essential area for improvement if trends for increasing incidence are to be reversed and better care provided for people with tuberculosis: 'Identify, facilitate access to, and ensure staff are aware of the appropriate isolation facilities and infection control precautions to be taken for patients with infectious, or potentially infectious TB, or who have drug resistant TB'. The recommendations provide the guidance the NHS needs to achieve this goal and prevent nosocomial infection.

9.3.2 Current practice

The review of current services collected the number of negative pressure units in service providers and aggregated these within HPU areas. There appears to be a positive relationship between the number of negative pressure units and number of notifications (see Figure 7).

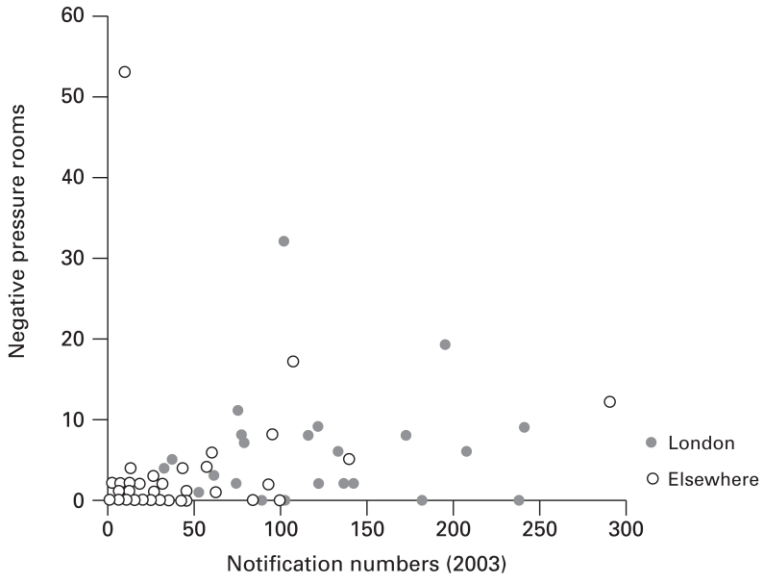

Figure 7 Negative pressure rooms vs. notified cases of TB per service provider

However, there seem to be errors in the reporting of the number of negative pressures units, which are much higher than expected, despite contacting the respondents to check. This discrepancy is too large to be accounted for by facilities being shared across HPU areas and counted twice, and so it seems that there is confusion among TB staff as to separate isolation rooms and negative pressure facilities. Given their use in cases of MDR TB, and the risk to other inpatients (with medicolegal implications), it would seem vital that staff working with TB are aware of the existing regulatory standards{105} regarding these facilities, and that it is made clear which isolation units meet these standards.

9.3.3 Methodological introduction

Studies were searched for which examined measures directed at patients with infectious suspected MDR TB to prevent transmission to other patients or contacts. (Measures to prevent transmission of TB to healthcare workers are addressed in chapter 13.)

Three retrospective cohort studies{233–235} were identified, all of which were performed in US hospitals after MDR TB outbreaks in wards of HIV-positive or AIDS patients. All hospitals introduced a range of infection control measures following the outbreaks.

There are a number of methodological considerations with regard to all three studies. Firstly, as multifaceted infection control programmes were implemented over time, it is difficult to assess the contribution to outcome of each individual infection control measure. Secondly, the implementation of control measures was associated with a decrease in the number of case patients; the effectiveness of these control measures in the presence of a high concentration of infectious patients with MDR TB over a long time period could not be fully evaluated. Finally, each study involved only small numbers of MDR TB patients in one hospital and was completely reliant on the accuracy of patients' medical and laboratory records.

9.3.4 Evidence statements

Although approximately equal numbers of AIDS patients had same-ward exposures with MDR TB patients before and after the implementation of infection control measures (which were in accordance with Centers for Disease Control and Prevention recommendations), the MDR TB attack rate was significantly lower in the period after implementation (8.8% *vs.* 2.6%, p=0.01).{234} (**2+**)

The proportion of patients with MDR TB decreased in a period when infection control measures were introduced compared with the period before (14% compared with 32% of patients; RR 0.5, 95%CI 0.2 to 0.9, p=0.02). Patients diagnosed during the intervention period were less likely than those diagnosed during the pre-intervention period to have had an identified nosocomial exposure to another case patient during a previous hospitalisation (10% compared with 67% patients; RR 0.2, p=0.003).{233} (**2+**)

Exposure before implementation of improved infection control measures to an infectious MDR TB patient on the HIV ward was recorded in 80% of MDR TB patients and 45% of MDR TB patients post-implementation. After implementation of control measures, no episodes of MDR TB could be traced to contact with infectious MDR TB patients on the HIV ward.{235} (**2+**)

9.3.5 From evidence to recommendations

The evidence for infection control measures in patients with smear-positive TB suspected to be MDR is limited. This applies to both HIV-negative and HIV-positive cases. One limitation of the studies analysed was that they often introduced several

measures at once, so the effect of a single action was not determinable. Secondly, measures were compared before and after an outbreak, when there may have been better application of the pre-existing infection control measures after such an outbreak, as well as the introduction of new measures.

Although MDR TB is no more infectious than fully drug-susceptible TB, the consequences of acquiring MDR TB are much more serious because of the greater difficulty and costs of treating it, with prolonged infectivity and the risk of much poorer outcomes. Immunosuppressed patients (particularly those HIV infected) are much more likely to acquire TB infection, and to progress to clinical disease.

The recommendations reinforce the essential role of negative pressure facilities in providing MDR TB care, based on a continuation of the practices previously recommended by the BTS.{6}

9.3.6 RECOMMENDATIONS

R73 Patients with suspected or known infectious MDR TB who are admitted to hospital should be admitted to a negative-pressure room. If none is available locally, the patient should be transferred to a hospital that has these facilities and a clinician experienced in managing complex drug-resistant cases. Care should be carried out in the negative-pressure room until the patient is found to be non-infectious or non-resistant, and ideally until cultures are negative. D(GPP)

R74 Staff and visitors should wear FFP3 masks,[13] during contact with a patient with suspected or known MDR TB while the patient is considered infectious. D(GPP)

R75 Before the decision is made to discharge a patient with suspected or known MDR TB from hospital, secure arrangements for the supervision and administration of all anti-TB therapy should have been agreed with the patient and carers. D(GPP)

R76 The decision to discharge a patient with suspected or known MDR TB should be discussed with the infection control team, the local microbiologist, the local TB service, and the consultant in communicable disease control. D(GPP)

[13] European standard EN149:2001; masks should meet the standards in 'Respiratory protective equipment at work: a practical guide HSG53' published by the Health and Safety Executive (2005). Available from www.hse.gov.uk

R77 Negative pressure rooms used for infection control in MDR TB should meet the standards of the Interdepartmental Working Group on Tuberculosis,{386} and should be clearly identified for staff, for example by a standard sign. Such labelling should be kept up to date. D(GPP)

Cross-referring:

For details of contact tracing in hospital in-patients, see section 12.7. Also see the algorithm in section 6.2.

9.4 Treatment of non-MDR TB resistance

9.4.1 Clinical introduction

This guideline concentrated on the evidence base for MDR TB through a systematic literature search and critical appraisal, but for completeness this subsection addresses the other forms of drug resistance. The GDG, having examined the evidence base for MDR TB, were in agreement that the guideline should reflect the guidance given by the BTS in 1998.{68} Treatment of patients with drug-resistant tuberculosis is carried out only by specialist physicians with appropriate experience in managing such cases.

Isolated streptomycin resistance

The recommended standard regimen for fully susceptible TB (see chapters 6 and 7) is unaffected.

Isolated isoniazid resistance

If this resistance is known before treatment commences, a regimen of rifampicin, pyrazinamide, ethambutol and streptomycin for two months followed by rifampicin and ethambutol for a further seven months gives good results by DOT.

If this resistance is found after treatment has been started, isoniazid may be stopped. Ethambutol, pyrazinamide and rifampicin should be given for two months followed by ethambutol and rifampicin for a further 10 months.

Isolated pyrazinamide resistance

Pyrazinamide resistance is usually due to infection by *M. bovis*. Ethambutol, isoniazid and rifampicin should be given for two months followed by isoniazid and

rifampicin for a further seven months. Isolated pyrazinamide resistance in *M. tuberculosis* infection should be treated with the same regimen.

Isolated ethambutol resistance

Isolated ethambutol resistance is uncommon. Isoniazid, pyrazinamide and rifampicin should be given for two months followed by isoniazid and rifampicin for a further four months.

Isolated rifampicin resistance

If rifampicin resistance is detected by either genetic probe or drug susceptibility testing, the patient should be isolated (see Fig 10) and treated as MDR TB until a full drug susceptibility profile of first-line drugs is available. Isolated rifampicin resistance is very uncommon but does occur and requires modification and extension of treatment to a period of 18 months, that is ethambutol, isoniazid and pyrazinamide for two months followed by isoniazid and ethambutol for a further 16 months. In approximately 90% of cases however, rifampicin resistance is not isolated and is a genetic marker for MDR TB.

Combined streptomycin and isoniazid resistance

This is the commonest dual resistance. This should be treated with the regimen for isolated isoniazid resistance found during treatment (see above).

Other non-MDR TB combinations

These are uncommon. Treatment would need to be individualised depending on the combination involved, and is best determined after discussion with a highly experienced clinician and the HPA Mycobacterium Reference Units.

9.4.2 RECOMMENDATION

R78 Patients with drug-resistant TB, other than MDR, should be under the care of a specialist physician with appropriate experience in managing such cases. First-choice drug treatment is set out in Table 31.

Table 31 Recommended drug regimens for non-MDR drug-resistant TB

Drug resistance	Initial phase	Continuation phase
S	2RHZE	4RH
H known before to treatment	2RZSE	7RE
H found after starting treatment	2RZE	10RE
Z	2RHE	7RH

E	2RHZ	4RH
R (only if confirmed isolated resistance)	2HZE	16HE
S+H	2RZE	10RE
Other	Individualised	
See Appendix D for details of the system of drug regimen abbreviations		

10 Management of latent tuberculosis

10.1 Treatment regimens for latent tuberculosis infection

10.1.1 Clinical introduction

Latent TB is defined in this guideline as infection with mycobacteria of the *M. tuberculosis* complex, where the bacteria are alive but not currently causing active disease. In people with latent TB, the rationale for treating those identified as infected by either Mantoux or IGTs is to kill any residual dormant bacilli in order to reduce or prevent later reactivation of tuberculosis disease. Single-agent isoniazid has been used in this role for at least 35 years, with considerable data on its efficacy in regimens of between six and 12 months.

In 2005, the Chief Medical Officer's TB Action Plan{2} set a goal of advising 'on the management of patients requiring preventive chemoprophylaxis according to national (currently British Thoracic Society) guidelines'. These guidelines should provide such advice, with an updated review of evidence in this field for clinicians in England and Wales.

10.1.2 Current practice

The review of current services found that the number of cases receiving treatment for latent TB infection correlated with neither the number of contacts nor new entrants screened. These data were aggregated across HPU localities to account for the different functions performed by different service providers. It would seem that different practices in contact tracing and new entrant screening have different yields in detecting or treating latent TB.

2006

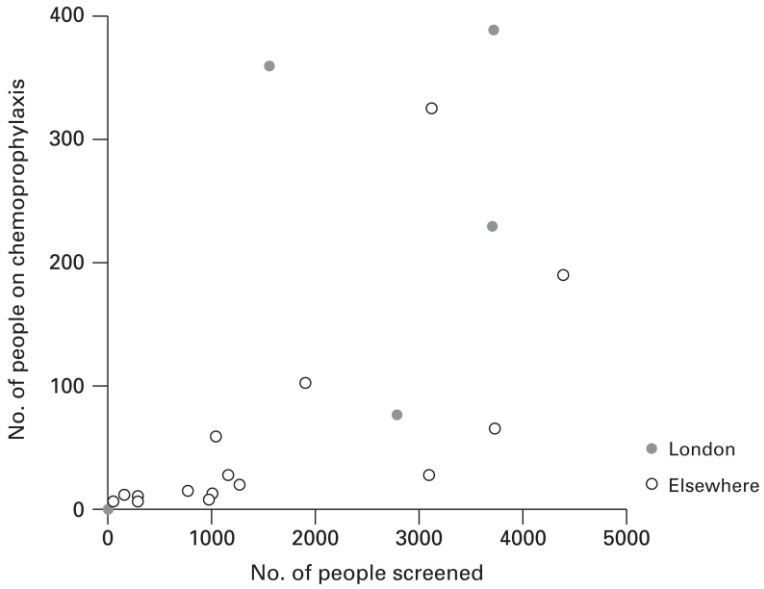

Figure 8Correlation of people screened against people given treatment for latent TB infection (chemoprophylaxis)

10.1.3 Methodological introduction

A detailed Cochrane review{236} looked at randomised trials of isoniazid of at least six months duration which were placebo controlled with at least two years follow-up, but excluded patients with known HIV infection. This review (11 trials totalling 73,375 patients) showed that durations of isoniazid of longer than six months had no additional benefit over that of six months (RR of 0.44, 95% CI 0.27 to 0.73 for six month, and 0.38, 95% CI 0.28 to 0.50 for 12 months). The toxicity of isoniazid was 0.26% of people on six months treatment and 0.52% of people treated for 12 months. Consideration of regimens for treatment of latent TB infection in this guideline was limited to those of six months' duration or shorter.

Two RCTs in adults with latent TB compared regimens of six months of prophylactic drug treatment with regimens of lesser duration in the prevention of the development of active TB. One study{237} compared rifampin given for three months, isoniazid and rifampin given for three months, isoniazid given for six months and placebo, in Chinese men with silicosis and Mantoux test results of greater than or equal to 10 mm of induration. The other study{238} compared isoniazid given for either three months or six months with placebo in tuberculin-positive participants with fibrotic lesions in seven European countries.

Several other studies compared regimens of six months of prophylactic treatment with isoniazid with two months of treatment with pyrazinamide and rifampin.{239–241} However, these studies were excluded as outcomes reported were adverse events and treatment completion rates and not the number of active TB cases which developed during follow-up.

Two studies in children were found. One RCT compared groups of tuberculin positive 5–15-year-olds in India who either did not receive prophylaxis, or received isoniazid for three months, rifampicin and isoniazid for one month, rifampicin and isoniazid for three months or isoniazid, rifampicin and pyrazinamide for one month.{242} This study however, was excluded due to methodological limitations. The only other study found in children was an observational study which described the use of various durations of isoniazid and rifampicin over a 15-year period in a UK health district and looked at active TB notification rates during this period.{243}

Three systematic reviews examined prophylaxis for TB in individuals with HIV infection.{244–246} The most recent of these reviews was a Cochrane review{246} which looked at preventive treatment for TB in comparison with placebo and additionally included studies which compared different regimens of preventive treatment (ie no placebo comparison). It included eleven trials with a total of 8,130 participants. This review replaced a previous Cochrane review.{247} The authors of the previous Cochrane review additionally published a systematic review of preventive treatment in HIV-infected individuals which included only studies which compared preventive treatment with placebo.{245} This study has been excluded as the four trials it included, plus several more, are all included in the updated Cochrane review {246} and in another systematic review published in 1999.{244} The 1999 systematic review{244} of isoniazid prophylaxis treatment compared with placebo has also been excluded to avoid double counting of trials as all of the studies it included (except two which have only been published as abstracts) are in the Cochrane review.{246}

The case definition of TB used varies across studies as does the proportion of cases with culture verification.

2006

10.1.4 Evidence statements

Efficacy

In a European study{238} of tuberculin-positive participants with fibrotic lesions in seven European countries, the risk of active TB was reduced by 21% by 12 weeks of isoniazid and 65% by 24 weeks when compared with placebo. The difference between the 12-week regimen and placebo was not statistically significant but the difference between the 12-week and the 24-week regimen was ($p<0.05$). (**1++**)

In a study in Hong Kong{237} of Chinese men with silicosis, the cumulative percentage of patients with active pulmonary TB over five years was compared in the patients who had received their prophylactic treatment without interruption. This percentage was higher in the placebo series than in the three treatment of latent TB infection groups combined ($p<0.01$) but there was no evidence of significant differences between the three treatment of latent TB infection regimens (placebo=27%, isoniazid and rifampin for three months=16%, isoniazid for six months=14% and rifampin for three months=10%). When the patients with extrapulmonary TB and those whose regimen was interrupted were included, the estimated rates at five years were 27% in the placebo series and 17% in the three treatment of latent TB infection series combined ($p<0.05$). (**1+**)

Treatment completion

In the European study{238} in the 12-week treatment groups, 87% completed isoniazid treatment and 91% placebo. These percentages were 78% and 82% respectively for the 24-week groups. (**1++**)

In the Hong Kong study,{237} 86% of participants in the three-month rifampin group, 76% in the isoniazid and rifampin three-month group, 74% in the six-month isoniazid group and 84% in the placebo group completed their allocated regimen without known interruption. (**1+**)

Adverse events

In the European study{238} the excess risk of hepatitis per 1,000 persons of isoniazid over placebo was 2.5 in the first 12 weeks and 1.1 in weeks 13–24. The number of hepatitis cases which could be avoided by shortening the duration of isoniazid from 24 weeks to 12 weeks would be 1.1 per 1,000 persons. (**1++**)

In the Hong Kong study{237} adverse effects were reported with a similar frequency in all four groups in the first 12 weeks. During this time, hepatic toxicity was reported in eight (1%) patients (three in the three-month isoniazid and rifampin group, three in the six-month isoniazid group and two in the placebo group) with only one (in the six-month isoniazid group) having symptomatic hepatitis. Only 4% of patients had their regimen stopped because of reactions. The serum alanine aminotransferase concentrations were higher in the three month isoniazid and rifampin and six month isoniazid series than in the three-month rifampin series ($p<0.001$) but there was no significant difference between the three-month rifampin series and placebo. (**1+**)

Children

In a study conducted in one health district in the UK{243} of children on treatment for latent TB infection, no child notified with TB in the period 1987–1996 (when shorter four month and three month regimens were introduced) had received treatment for latent TB infection previously. Furthermore, no child on treatment for latent TB infection required their three or four month regimen of isoniazid and rifampicin treatment to be stopped for possible side effects during the nine year period since the introduction of these regimens. (**3**)

People with HIV: development of active TB

A Cochrane systematic review{246} found that preventive therapy (any anti-TB drug) *vs.* placebo was associated with a lower incidence of active TB (RR 0.64, 95%CI 0.51 to 0.81). All drug regimens regardless of type, frequency or duration of treatment, reduced the incidence of active TB compared with placebo and no differences were found between active regimens in terms of effectiveness. (**1++**)

The review{246} found that among individuals who were tuberculin skin test positive, preventive therapy reduced the risk of active TB by 62% (RR 0.38, 95%CI 0.25 to 0.57). Although a similar trend was found for individuals with a negative tuberculin test these results were not statistically significant. (**1++**)

People with HIV: all-cause mortality

The review{246} found no evidence that preventive therapy versus placebo reduced all-cause mortality. (**1++**)

People with HIV: incidence of adverse drug reactions

Compared to placebo, preventive therapy led to more adverse events resulting in stopping treatment (RR 2.49, 95%CI 1.64 to 3.77). The likelihood of stopping treatment due to adverse effects was higher for combination therapies than for isoniazid monotherapy compared with placebo (eg for isoniazid *vs*. placebo: RR 1.66, 95%CI 1.09 to 2.51 whilst for isoniazid and rifampicin *vs*. placebo: RR 16.72, 95%CI 3.29 to 84.9).{246} (**1++**)

10.1.5 From evidence to recommendations

A European study{238} found six months isoniazid to be more effective than three months whilst a Hong Kong study{237} found no difference in effectiveness between isoniazid and rifampin for three months (3RH) and isoniazid for six months (6H) in those who were not HIV positive. Therefore, either 6H or 3RH could be used.

The Hong Kong study also demonstrated no difference between these two regimens and three months of rifampicin. In the UK, six months of rifampicin has been demonstrated to be effective, and the GDG recommended a six-month course to avoid any risk of rifampicin-resistant strains developing.

In 2000 a regimen of rifampicin and pyrazinamide for two months (2RZ) was recommended for treatment for latent TB infection in the USA.{248} In the UK, although this 2RZ regimen was felt to have equivalent efficacy to a regimen of three months rifampicin and isoniazid (3RH), because it was predicted to have significantly higher toxicity, the 2RZ regimen was not recommended for use in the UK.{68} Subsequent experience in clinical practice in the USA confirmed significant hepatotoxicity, including deaths, in clinical practice,{249–251} which led in 2003 to the American Thoracic Society and the Centers for Disease Control advising that this regimen no longer be routinely used for treatment for latent TB infection.{250}

There was no high-level evidence in neonates or children, so recommendations are based on clinical experience. The recommendations shown below were drawn up to reflect the group consensus.

A Cochrane review{246} in HIV-positive people found in those who were tuberculin positive, preventive therapy reduced the risk of active TB. A similar but non-

significant trend was found for individuals with a negative Mantoux test. The likelihood of stopping treatment due to adverse effects was higher for combination therapies than for isoniazid monotherapy, therefore the latter has been recommended in this population.

People should be selected for treatment for latent TB infection by the risk factors set out in section 10.1. Risk of hepatotoxicity from these drugs increases with age. Although there was no evidence to recommend an age threshold, it has been common practice in the UK not to advise treatment for latent TB infection for otherwise eligible people who are over the age of 35, as the risk may start to outweigh the potential benefit.

All the recommendations identify people on the basis of the two-step testing process for latent TB which is recommended in section 5.1. Obvious exceptions will occur when, for example, the patient is immunocompromised and Mantoux test is not reliable, and clinical judgement will be required.

The recommendations state that treatment for latent TB infection with 3RH or 6H regimens would be ineffective in contacts of people with MDR TB. In these and other cases where treatment for latent TB infection is not recommended, 'inform and advise' information is needed. Follow-up is also recommended for contacts of a person with MDR TB.

2006

10.1.6 RECOMMENDATIONS

2006, amended 2011

R79 Treatment of latent TB infection should be considered for people in the following groups, once active TB has been excluded by chest X-ray and examination: D(GPP)

- people identified through screening who are:
  - 35 years or younger (because of increasing risk of hepatotoxicity with age[14])
  - any age with HIV
  - any age and a healthcare worker

and are either:

  - Mantoux positive (6 mm or greater), and without prior BCG vaccination, *or*

[14] For people aged 36 or older, consider risks and benefits for the individual before offering treatment.

– strongly Mantoux positive (15 mm or greater), interferon-gamma positive, and with prior BCG vaccination

- children aged 1–15 years identified through opportunistic screening, to be:
  – strongly Mantoux positive (15 mm or greater), *and*
  – interferon-gamma positive (if this test has been performed), *and*
  – without prior BCG vaccination
- people with evidence of TB scars on chest X-ray, and without a history of adequate treatment.

2006, amended 2011

R80 People with HIV who are in close contact[15] with people with sputum smear-positive respiratory TB should have active disease excluded and then be given treatment for latent TB infection (see R10-13).

R81 Treatment for latent TB infection should not be started in close contacts of people with sputum smear-positive MDR TB who are strongly Mantoux positive (15 mm or greater), as no regimen is of proven benefit, and only a small proportion of people infected will develop the disease. Long-term monitoring should be undertaken for active disease. D(GPP)

R82 People who have agreed to receive treatment for latent TB infection should be started on one of the following regimens: C

2006

- either six months of isoniazid (6H) or three months of rifampicin and isoniazid (3RH) for people aged 16–35 not known to have HIV A
- either six months of isoniazid (6H) or three months of rifampicin and isoniazid (3RH) for people older than 35 in whom treatment for latent TB infection is recommended (see R62) and who are not known to have HIV D(GPP)
- six months of isoniazid (6H) for people of any age who have HIV A
- six months of rifampicin (6R) for contacts, aged 35 or younger, of people with isoniazid-resistant TB. D(GPP)

[15] Close contacts may include a boyfriend or girlfriend and frequent visitors to the home of the index case, in addition to household contacts.

2006

People eligible for treatment of latent TB infection, but who decline to take this treatment, should be given 'inform and advise' information about TB and have chest X-rays three and 12 months later. D(GPP)

2006, amended 2011

R83 Neonates who have been in close contact with people with sputum smear-positive TB who have not received at least two weeks' anti-tuberculosis drug treatment should be treated as follows. D(GPP)

- The baby should be started on isoniazid (refer to the current ‘British national formulary for children’) for three months and then a Mantoux test performed after three months' treatment.
- If the Mantoux test is positive (6 mm or greater) the baby should be assessed for active TB (see section 5.2). If this assessment is negative, then isoniazid should be continued for a total of six months.
- If the Mantoux test is negative (less than 6 mm), it should be repeated together with an interferon-gamma test. If both are negative then isoniazid should be stopped and a BCG vaccination be performed (see chapter 11).

R84 Children older than four weeks but younger than two years who have not had BCG vaccination and are in close contact with people with sputum smear-positive TB should be treated as follows. D(GPP)

- The child should be started on isoniazid (refer to the current ‘British national formulary for children’) and a Mantoux test performed.
- If the Mantoux test is positive (6 mm or greater), the child should be assessed for active TB (see section 5.2). If active TB is ruled out, full treatment for latent TB infection should be given (see R86).
- If the Mantoux test is negative (less than 6 mm), then isoniazid should be continued for six weeks, and then a repeat Mantoux test together with an IGT test should be carried out.
- If the repeat tests are negative, isoniazid may be stopped and BCG vaccination performed (see chapter 11).

- If either repeat test is positive (6 mm or greater), then the child should be assessed for active TB (see section 5.2.) and consider treating for latent TB. Contact tracing for children younger than two years when the index case is sputum-smear-positive is summarised in an algorithm (section 12.2).

R85 BCG-vaccinated children aged older than four weeks but younger than two years, in close contact with people with sputum-smear-positive respiratory TB, should be treated as follows. D(GPP)

- The child should have a Mantoux test. If this is positive (15 mm or greater), the child should be assessed for active TB (see section 5.2). If active TB is excluded, then treatment for latent TB infection should be given (see R86).
- If the result of the test is as expected for prior BCG (less than 15 mm), it should be repeated after six weeks together with an interferon-gamma test.
- If the repeat Mantoux test is also less than 15 mm, and the interferon-gamma test is also negative, no further action is needed.
- If the repeat Mantoux test becomes more strongly positive (15 mm or greater and an increase of 5 mm or more over the previous test), or the interferon-gamma test is positive the child should be assessed for active TB (see section 5.2). If active TB is excluded, treatment for latent TB infection should be given.

R86 For children requiring treatment for latent TB infection, a regimen of either three months of rifampicin and isoniazid (3RH) or six months of isoniazid (6H) should be planned and started, unless the child is known to be HIV positive, when 6H should be given (see R82). D(GPP)

R87 Healthcare workers should be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including people who: D(GPP)

- are HIV positive
- are injecting drug users
- have had solid organ transplantation

2006, amended 2011

2006

- have a haematological malignancy
- have had a jejunoileal bypass
- have chronic renal failure or receive haemodialysis
- have had a gastrectomy
- are receiving anti-tumour necrosis factor (TNF)-alpha treatment
- have silicosis.

Patients in these groups should be advised of the risks and symptoms of TB, on the basis of an individual risk assessment basis, usually in a standard letter of the type referred to as 'inform and advise' information.

Cross-referring:

For details of excluding active TB, see section 5.2.

For details of DOT, see section 8.2.

For details of approaches to improving adherence, see section 8.3.

For details of active case finding, including contact tracing, see chapter 12.

For examples of 'inform and advise' information, see Appendix H.

10.2 Risk factors for tuberculosis infection: selecting people for treatment for latent tuberculosis infection

10.2.1 Clinical introduction

The risk of developing clinical TB depends on both the risk of becoming infected, and the risk that after acquiring infection this will progress to disease. This section addresses the latter risk.

Further considerations are the age at which initial infection occurs and time since initial infection. Infection earlier in life, particularly under age five, may be associated with increased risks of progression and dissemination of disease. The greatest chance of progressing to disease is within the first two years after infection, with half of all cases of disease occurring within five years of the original infection.{252} There however remains a lifelong risk of progression to disease for all those with 'dormant' organisms. Such people are a minority of infected patients. International data shows,{253} that whilst some 32% of the world's population (1.9 billion) was estimated infected as judged by a positive Mantoux test, only some 8–11 million persons per year are estimated to develop clinical disease.

Many more studies exist which examine the risk factors for active tuberculosis in groups irrespective of tuberculin skin test status. These studies do not show whether such groups are more likely to develop latent infection, or if infected progress to clinical disease, or whether both mechanisms apply.

Treatment for latent TB infection can be either secondary, after latent infection has occurred (see section 10.1), or primary to try to prevent the acquisition of infection after exposure. Most studies concentrate on secondary treatment for latent TB infection, but there are circumstances where primary treatment for latent TB infection may be appropriate, for example exposure of neonates to sputum smear-positive parents, or of people with HIV to people with sputum smear-positive TB.

10.2.2 Current practice

The Health Protection Agency's systems of notification and enhanced surveillance (see chapter 14 for details) do not collect data on cases of latent tuberculosis, or on people screened and found to be uninfected.

The review of current services followed-up respondents reporting more than five people screened for latent tuberculosis in 2003, and sought a breakdown between those who were new entrants and those who were contacts of people with infectious TB. Although all the clinics that were followed-up were able to provide some response, in the majority they reported that they could not derive such detail from the data that they had collected locally. Many reported ongoing work to improve their local collection of data on screening.

10.2.3 Methodological introduction

The evidence was examined to consider which TB-infected population groups are the most likely to progress from infection to active TB. This information identifies those who would benefit most from treatment for latent TB infection.

Few studies considered the risk of developing active TB in those known to have (or highly likely to have) latent infection, probably because these groups are likely to receive treatment for latent TB infection (except in older studies). Furthermore, these studies do not in general have a tuberculin-positive control group without the risk factor, so it is not possible to calculate relative risks, only incidence rates.

Additionally, the consideration of HIV infection as a risk factor for active TB in those with latent infection is problematic. This is due to the difficulties of diagnosing latent tuberculosis in this population using conventional skin test methods.

Many more studies exist which examine the risk factors for active TB in groups irrespective of Mantoux test status. It is unclear, however, whether these groups are more likely to develop latent tuberculosis or once they had infection, are at a higher risk of progressing to active TB, both of which could be explanations for these groups having a high rate of active TB compared to control groups.

10.2.4 From evidence to recommendations

The GDG discussed the issues and agreed that, rather than attempting to synthesise all the evidence in this area, it would be more useful to provide tables of risk factor data. These tables, modified from the American Thoracic Society official statement of 'targeted tuberculin testing and treatment of latent infection'{248} are shown below. Table 32 ranks a range of active TB incidence rates in tuberculin-positive persons with certain risk factors/medical conditions. Table 33 (overleaf) ranks a range of relative risks of active tuberculosis, in populations with certain risk/factors/medical conditions, independent of Mantoux test status.

While people who are underweight and/or have diabetes are at increased relative risk of TB, the GDG did not feel that it would be appropriate to alert them all to the symptoms and signs of TB as their absolute risks of TB are very low.

10.2.5 RECOMMENDATIONS

The evidence supporting this section informed the recommendations given in section 10.1.

Table 32: Incidence of active TB in persons with a positive tuberculin test by selected risk factors

Risk factor		**TB cases/1,000 person-years**
HIV infection{254}		35.0–162
Injecting drug use{255}	HIV seropositive	76.0
	HIV seronegative or unknown	10.0
Silicosis{237}		68.0
Recent latent tuberculosis{256}	Infection <1 year past	12.9

	Infection 1–7 years past	1.6
Radiographic findings consistent with prior TB{257–259}		2.0–13.6
Weight deviation from standard{260}	Underweight by >15%	2.6
	Underweight by 10–14%	2.0
	Underweight by 5–9%	2.2
	Weight within 5% of standard	1.1
	Overweight by >5%	0.7

2006

Table 33: Relative risk for developing active TB by selected clinical conditions

Clinical condition		**Relative risk**
Solid organ transplantation	Renal{261}	37
	Cardiac{262},{263}	20–74
Jejuno-ileal bypass{264},{265}		27–63
Silicosis{266}		30
Chronic renal failure/haemodialysis{267–269}		10–25.3
Gastrectomy{270–272}		2.5
Diabetes mellitus{273–275}		2.0–41
Anti-TNF-alfa treatment{276},{277}		4–8
Contact smear-positive TB{278}		5–10

11 BCG vaccination

11.1 Overview

11.1.1 Overall introduction

Bacille Calmette-Guerin (BCG) was developed by Calmette and Guèrin, at the Pasteur Institute (Lille) using *in vitro* attenuation by repeated passage of an isolate of *M. bovis* from 1908 onwards; it was finally tested in humans in 1921. Since BCG has never been cloned and has been grown under different conditions and in different laboratories, genetic differences have developed between the various commercially used strains,{279} so called 'antigenic drift'. Genome research has since shown that in the passaging of the organism, but before its distribution from the Pasteur Institute, a section of the genome, the RD1 region, was deleted. This deleted region common to all BCG strains contains antigens such as ESAT6, CFP10 and tb7.7 which are now used in interferon-gamma based blood tests, and hence these blood tests are not affected by prior BCG vaccination (see section 5.1 for further details).

The efficacy of a vaccine is a measure of its activity on individuals given the vaccine and can be defined as the proportion of those vaccinated who gain protective immunity from the vaccination.{280} Huge variations in estimates of efficacy against pulmonary TB, ranging from 0% to >80%, have been shown for different BCG vaccines in various geographical settings.

While a number of explanations have been put forward for this, geographical latitude seems to have a particularly important effect, accounting for over 40% of the variability in efficacy.{281} Thus nearly zero efficacy against tuberculosis in India,{282} is contrasted with a 64% protective efficacy in people of Indian origin with the same vaccine in a higher, more temperate, latitude.{283} Though the effect of climate on environmental mycobacteria has been suggested as the cause of the latitude effect, this has not been proven.

A further conundrum in BCG efficacy is that even in parts of the world where there is little reported efficacy against tuberculosis, efficacies of 50–60% are reported against leprosy and Buruli ulcer, caused by other mycobacteria.{280} Yet another problem with interpreting the data is that although it was assumed that the tuberculin sensitivity induced by BCG vaccination correlated with protective efficacy, this is not so. In a large UK study there was no correlation between tuberculin sensitivity induced by BCG and protective efficacy; those individuals tuberculin negative after BCG vaccination derived just as much protection as those who became tuberculin positive.{284}

Many controlled trials have followed efficacy for 10–15 years and have shown some decline over time, but the total duration of any benefit was not known and could only be expressed as an efficacy lasting up to 15 years.{285} The only truly long-term follow-up of BCG vaccination, in a North American aboriginal population, reported in 2004, showed 50% protective efficacy lasting for at least 50 years.{286}

BCG is a live vaccine and as such is contraindicated{3} in a number of situations where the immune system may be compromised, particularly if the person is known or suspected to be HIV positive, because of the risk of generalised BCG infection. HIV testing, after appropriate counselling, is also an important consideration, but lies outside the scope of this guideline. Readers should be aware of the British HIV Association guidelines on TB/HIV co-infection{8} and those forthcoming on testing from the British Association for Sexual Health and HIV.

Current practice in vaccination is led by the advice of the Joint Committee on Vaccination and Immunisation, principally through the 'Green Book'.{3},{21}

11.1.2 OVERALL RECOMMENDATIONS

R88 When BCG is being recommended, the benefits and risks of vaccination and remaining unvaccinated should be discussed with the person (or, if a child, with the parents), so that they can make an informed decision. This discussion should be tailored to the person, be in an appropriate language, and take into account cultural sensitivities and stigma. D(GPP)

R89 People identified for BCG vaccination through occupational health, contact tracing or new entrant screening who are also considered to be at increased risk of

being HIV positive, should be offered HIV testing before BCG vaccination[16]. (See section 10.1 for details of further action in HIV-positive patients.) D(GPP)

11.2 For neonates

11.2.1 Clinical introduction

Neonatal BCG (up to age three months) is given in countries, or in subgroups defined by ethnicity and/or deprivation, with high rates of TB disease. Efficacy studies on neonatal BCG have used different end points which have contributed to some confusion about its efficacy in various settings. These have included the end points of pulmonary disease, death, TB meningitis, disseminated (miliary) disease, and laboratory-confirmed cases.

In England and Wales, which has had a selective neonatal BCG programme for over 20 years, assessments of coverage of appropriate infants have shown substantial variation in, and deficiencies in, both BCG policy and implementation.{287} These deficiencies and system problems were particularly in medium and low TB incidence districts which often had no system for identifying those neonates for whom BCG was recommended.

11.2.2 Current practice

The DH advises BCG vaccination for all neonates at higher risk of TB, with opportunistic vaccination of older children as necessary, according to criteria set out below in the recommendations.

The review of current services, conducted in the year prior to the introduction of neonatal vaccination and abolition of school-based vaccination, found that outside London, only two of 62 clinics (3%) (in the same HPU, an area of high notifications) reported universal neonatal BCG vaccination. In London, 12 of 31 clinics (39%) reported universal coverage. There was no consistency in the risk groups used for selected neonatal BCG. Many respondents did not name any explicit risk groups, but those who gave details mostly cited ethnicity, immigration and family history as the means for identifying neonates at higher risk.

2006

[16] See the British HIV Association guideline for details of further action in HIV-positive patients. Available from www.bhiva.org.

11.2.3 Methodological introduction

Studies investigating the effectiveness of BCG vaccination administered in neonates and infants in preventing the development of TB infection or disease were sought. This was compared to unvaccinated groups in relevant populations. One meta-analysis, one cohort study and one case control study were found.

One meta-analysis conducted in the USA{288} included five RCTs and 11 case control studies in the analysis. The scope was international, but all RCTs were conducted in the northern hemisphere and were situated far from the equator relative to case controls, which were distributed across both temperate and equatorial regions. The analysis combined RCT and case control studies separately and did not use cross-design analysis since there were too few RCTs relative to case control studies. It was therefore appropriate to grade the evidence statements according to whether they were derived from the RCT (level 1) or case control results (level 2).

Factors for consideration raised by the meta-analysis included the following:

- The duration of BCG vaccination protection administered in infancy was inadequately established despite information on this issue being available from six studies. This was due to the small numbers of TB cases when data was analysed separately by year of occurrence.
- The impact of BCG strain on efficacy of immunisation was not associated with variation in the protection afforded by the vaccine in the studies reviewed.
- Differences in the characteristics and methodological quality of individual studies were addressed by a sensitivity analysis, expressed as a study quality validity score.
- Study quality validity scores accounted for 15.3% of the heterogeneity in the results of the nine case control studies, while RCTs were homogeneous.
- Distance from the equator did not appear to be an important correlate of BCG efficacy reported by case control studies, while RCTs displayed homogeneity in terms of distance from the equator.

One cohort study conducted jointly in the Federal Republic of Germany (FRG) and the German Democratic Republic (GDR),{289} was published prior to the meta-analysis, but not cited in it. The study retrospectively focused on BCG vaccination

administered to an entire population of neonates in the GDR over a three and a half year period compared to no vaccination in the FRG over the same time period to investigate the efficacy of the vaccine in preventing cases of TB meningitis.

A case control study conducted in Spain,{290} which was not cited in the meta-analysis was excluded due to methodological limitations presented in Appendix I.

11.2.4 Evidence statements

Evidence was found for the efficacy of BCG vaccination in infancy for preventing:

- pulmonary TB disease
- TB deaths
- TB meningitis
- laboratory-confirmed TB cases
- disseminated TB.

Evidence for these five outcomes is presented in Table 34.

Table 34: Summary of evidence: neonatal BCG vaccination

Outcomes	Intervention: BCG vaccinated *vs.* unvaccinated infants	Results	Association/statistical significance	Ref and NICE grade
Pulmonary TB disease	Four RCTs	Protective effect 0.74	Combined RR 0.26 (95% CI 0.17 to 0.38, p< 0.05)	{288} 1+
	Nine case control studies	Protective effect 0.52	Combined OR 0.48 (95% CI 0.37 to 0.62, p<0.05)	{288} 2+
TB deaths	Five RCTs	Protective effect 0.65	Combined RR 0.35 (95% CI 0.14 to 0.88, p<0.05)	{288} 1+
TB meningitis	Five case control studies	Protective effect 0.64 (based on 181 cases of TB meningitis)	Combined OR 0.36 (95% CI 0.18 to 0.70, p<0.05)	{288} 2+
	One cohort study	0/770,000 intervention *vs.* 57/2,100,000 (0.0048%) control cases developed TB disease	Not reported	{289} 2+
Laboratory-confirmed TB	Three case control studies	Protective effect 0.83 (based on	Combined OR 0.17 (95% CI 0.07 to 0.42,	{288} 2+

2006

cases		results of 108 TB cases confirmed by either histology or culture)	p<0.05)	
Disseminated TB	Three case control studies	Protective effect 0.78	Combined 0.22 (95% CI 0.12 to 0.42, p<0.05)	{288} 2+

11.2.5 Health economics

The GDG considered the interactions between neonatal and school-age BCG vaccination programmes required population dynamic economic modelling, which is, at the time of writing, being commissioned by the DH. With this in mind, recommendations on neonatal BCG are presented purely on the basis of clinical evidence, pending the findings of the model.

11.2.6 From evidence to recommendations

Neonatal BCG is significantly better than no vaccine using the end points of pulmonary disease, death, meningitis, laboratory-confirmed TB and disseminated TB.

There is difficulty ensuring thorough vaccination coverage in primary care, where babies are not registered until the first appointment, compared to vaccination by midwives, for example, where coverage can be assured.

The GDG supported the explicit criteria set out by the WHO for discontinuing universal vaccination, but wished TB clinicians and service planners to be aware of possible future changes to the criteria in response to changing global epidemiology. The aim of this section is to guide clinicians in vaccinating those who are most at risk.

Given the conclusions of the health economics for school-based BCG vaccination in section 11.3, the recommendations seek to provide guidance for a neonatal BCG programme that will offer protection to all who are at risk. In a high-incidence area, this may be most easily provided by a universal programme.

The largest group of neonates who are at increased risk of TB are those whose families have immigrated from high-incidence countries. Neonates continue to be at risk even if their parents were also UK born because of continuing migration, home visits and exposure to increased levels of TB within communities. The

recommendations therefore advise selection on the basis of a parent or a grandparent being born in a high-incidence country. GDG members were aware of selection being practised on the basis of skin colour or surname, and aimed to provide clear-cut recommendations to replace these practices.

In accordance with the Green Book,{3} tuberculin skin testing is not routinely recommended prior to BCG vaccination for children under six years of age.

11.2.7 RECOMMENDATIONS

R90 Neonatal BCG vaccination for any baby at increased risk of TB should be discussed with the parents or legal guardian. D(GPP)

R91 Primary care organisations with a high incidence of TB[17] should consider vaccinating all neonates soon after birth. D(GPP)

R92 In areas with a low incidence of TB[17], primary care organisations should offer BCG vaccination to selected neonates who: D(GPP)

- were born in an area with a high incidence of TB[17],[17][17] or
- have one or more parents or grandparents who were born in a high-incidence country,[18] or
- have a family history of TB in the past five years.

R93 Mantoux testing should not be done routinely before BCG vaccination in children younger than six years. D(GPP)

Cross-referring:

For details of identifying the Mycobacterium species prior to large-scale contact tracing, see section 5.3

11.3 For infants and older children

11.3.1 Clinical introduction

Following clinical trials in the early 1950s, BCG vaccination was introduced for previously unvaccinated adolescents aged 10–14.{284} Age 10–14 was selected for vaccination in 1953 because at that time, in what was nearly entirely a white UK-

2006

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[17] As defined by the HPA; go to **www.hpa.org.uk** and search for 'tuberculosis rate bands'.
[18] Go to **www.hpa.org.uk** and search for 'WHO country data TB'.

born population, TB was most common in those aged 15–29 (with a second peak in older people). This cohort, now aged over 70, have the highest TB rates among white UK-born people (see Appendix G). The rationale therefore was to give vaccination at this age to try to prevent acquisition of pulmonary disease before this peak, and it became known as the 'Schools BCG Programme'. During the writing of this guideline, the DH abolished the programme, replacing it with neonatal vaccination based on the criteria given above.

Tuberculosis rates fell through the 1950s and early 1960s by almost 10% per annum, and continued to fall at a lower rate until 1987 (approximately), since when there has been an increase. However, over this time, both the proportion of cases and rates of disease in the white UK-born ethnic group have continued to fall. The proportion of cases in this ethnic group was 85% in 1985, 43% in 1993, 37% in 1998, and is now under 30%.{140} Rates of TB in white UK-born children aged 10–14 years, the cohort of previously unvaccinated children to whom the schools programme applies, are between one and two cases per 100,000 for both sexes (see Appendix G).

International criteria for discontinuation of unselective BCG vaccination

The International Union against Tuberculosis and Lung Disease published their criteria for discontinuation of BCG programmes in countries of low prevalence in 1993.{291} This set out general considerations and criteria. The general criteria to be met in a country before stopping or modifying BCG programmes were:

- there is a well functioning TB control programme
- there has been a reliable monitoring system over the previous five years or more enabling the estimation of the annual incidence of TB by age and risk groups, with particular emphasis on TB meningitis and sputum smear-positive pulmonary TB
- due consideration has been given to the possibility of an increase in the incidence of TB resulting from HIV infection.

The criteria for discontinuing a BCG vaccination programme in a country with a low prevalence of TB were:

2006

- the average annual notification rate of sputum smear-positive pulmonary TB should be five cases/100,000 population or less during the previous three years, *or*
- the average annual notification rate of TB meningitis in children under age five years of age should be less than 1 case per 10 million general population over the previous five years, *or*
- the average annual risk of TB infection should be 0.1% or less.

Additional considerations were also suggested.

Cost: with it being advisable, but not essential, to calculate the number of cases which would be prevented by continuing BCG vaccination, so that the saving can be expressed in terms of preventing human suffering and also in saving of cost of treatment.

Adverse reactions to BCG: documentation of the rate of adverse reactions to BCG vaccination in a country are helpful. A low incidence rate of active tuberculosis, coupled with a high rate of adverse reaction tends to reinforce a decision to stop or modify the BCG vaccination programme. The reported rates of serious adverse reactions varies from country to country, with vaccination technique used, the preparation of BCG vaccination used, and doctors' awareness of reactions being factors influencing the reported rates.

Risk groups: in the event of discontinuation of the BCG vaccination programme for the general population, it may be advisable to continue vaccination in certain well-defined population groups with a known high notification rate of active tuberculosis.

11.3.2 Current practice

The Department of Health no longer recommends BCG vaccination for school children between ages 10–14 years.

11.3.3 Methodological introduction

The focus was on studies investigating the effectiveness of BCG vaccination administered in a school-aged population in preventing TB infection or disease. One RCT and two cohort studies were found that addressed the topic.

2006

One RCT conducted in the UK{285} reported on the protective efficacy of BCG vaccination against tuberculosis (TB) disease in vaccinated and unvaccinated groups of school-aged subjects in England over a 20-year follow-up period. Two cohort studies, both conducted in the UK,{292},{293} retrospectively identified notified cases of TB disease who had been eligible for BCG vaccination within the schools vaccination scheme when aged 13.{292},{293} These studies estimate the protective efficacy of the BCG vaccine in this general population and in the white ethnic group. Sutherland and Springett{292},{293} estimate the numbers of additional TB notifications that would be expected among young white adults annually, if the schools BCG scheme were to be discontinued at specific dates. Both cohort studies incorporated data from the RCT cited above.

11.3.4 Evidence statements

Efficacy of BCG vaccination for preventing TB disease

One RCT{285} and one cohort study{292} found that BCG given in school-aged children led to a reduction in the annual incidence of TB disease in vaccinated compared to unvaccinated individuals. Evidence is presented in Table 35.

Table 35: Summary of evidence: vaccinated and unvaccinated children of school-going age

BCG vaccinated *vs.* unvaccinated results	Statistical significance	Ref and NICE grade
Protective efficacy 0.77; average annual incidence 0.23 per 1,000 versus 0.98 per 1,000 (20 years follow-up)	Not reported	{285} 1+
1949–1981: Protective efficacy 0.80 (ages 15–19), 0.75 (ages 20–24)	Not reported	{292} 2+
1983: Protective efficacy 0.75 (ages 15–24); notification rate 3.3 per 100,000 versus 13.2 per 100,000	Not reported	{292} 2+

BCG vaccination in school-aged children and longitudinal trends in TB prevention

Evidence was found on BCG vaccination use in school-aged children in England and Wales and the following longitudinal trends:

- decrease in the efficacy of BCG and the incidence of TB notifications
- the estimated risk of notified TB in the white ethnic population eligible for the school's BCG vaccination scheme

2006

- TB notifications prevented by BCG vaccination in the white school-aged population
- TB notifications as a consequence of discontinuing the BCG schools vaccination scheme for the white ethnic population
- the estimated risk of notified TB in the white ethnic group if the school's BCG vaccination scheme were discontinued.

The evidence is presented in Table 36.

Table 36: Summary of evidence: vaccination and longitudinal trends in TB among children of school-going age

BCG use and longitudinal trend	Results Vaccinated *vs.* unvaccinated groups/BCG discontinued *vs.* continued	Statistical significance	Ref and NICE grade
Progressive decrease in protective efficacy in successive five-year follow-up periods	0.40, 0.33, 0.10, 0.09 *vs.* 2.50, 1.06, 0.26, 0.08 per 1000	p=0.01	{285} 1+
Annual decrease in TB notification rates in three cohorts covering a 29-year period	Ages 15–19: 5% *vs.* 10%	Not reported	{292} 2+
	Ages 20–24: 7% *vs.* 11%		
Estimated risk of notified TB between ages 15 and 30 in white UK-born people eligible for BCG schools programme	1984: 1/6,500 (BCG administered at age 13) *vs.* 1/700 (Mantoux test negative)	Not reported	{293} 2+
	1994: 1/17,000 (BCG administered at age 13) *vs.* 1/4,300 (Mantoux test negative)		
Estimated TB notifications prevented by BCG vaccination in the white school-aged population	1983: 557 at ages 15–29 due to 7.65 million vaccinations in previous 15 years	Not reported	{293} 2+
	1988: 370 at ages 15–29 due to 7.65 million vaccinations in previous 15 years		
Additional TB notifications due to discontinuing BCG schools vaccination in the white ethnic population	Discontinuation in 1986: 129 in 2,003 (ages 15–29)[19]	Not reported	{293} 2+
	Discontinuation in 1996: 51 in 2,013 (ages 15–29)		
Estimated risk of notified TB in the white ethnic population if BCG schools vaccination were discontinued	Discontinuation in 1986: 1/2,200 between ages 15 and 30 (first wholly unvaccinated five-year cohort aged 13 in 1987–91) *vs.* 1/2,700	Not reported	{293} 2+
	Discontinuation in 1996: 1/5,400 between ages 15 and 30 (five-year cohort aged 13 in 1997–2001) *vs.* 1/6,900		

2006

[19] Some of these would be secondary additional notifications outside the age group 15–29 years of age.

11.3.5 Health economics

A decision analytic model was used to estimate the cost-effectiveness of the current school BCG programme. The model distinguished between a 'high-risk' group of children who should have already been offered BCG before the school programme (through neonatal or new entrant schemes) and a 'low-risk' group, which is the remainder of the 10–14-year-old cohort. The school BCG programme is potentially beneficial for low-risk children and as a catch-up for previously unvaccinated high-risk children. The model relies on the assumption that there is negligible transmission between the high-risk and low-risk groups.{294}

The model is a simple decision tree that estimates the number of primary cases for a cohort of 10–14-year-olds, the consequent number of secondary cases in the population, and the associated costs and health outcomes, with and without a school BCG programme. The effectiveness of school BCG for the low-risk group and the number of secondary cases per primary case were taken from Saeed *et al* (2002),{295} updating the work of Sutherland and Springett in 1989.{293} The benefits for unvaccinated high-risk children were then estimated. It is important to note that this method can only give approximate results for an infectious disease such as TB. A population dynamic model would be expected to provide more reliable results.

Whenever possible, the input parameters and assumptions for the model were based on best available empirical evidence. However, we could not find evidence to inform all of the important parameters. In such cases, estimates are based on judgement by the guideline economist and the GDG. There is some uncertainty over the results of the model due to uncertainty over some of the input parameters for the analysis. In particular, the results are sensitive to the proportion of 10–14-year-olds in 'high-risk' groups, the estimated QALY loss due to TB, and the estimated cost of treating a case of TB.

Cost-effectiveness of school BCG for the low-risk group

The economic model suggests that the schools programme is not cost-effective for the low-risk group alone – with 0% in the high-risk group, the incremental cost per QALY gained (incremental cost-effectiveness ratio, ICER) is over £150,000 if we assume 15-year protection from BCG, and over £750,000 if we assume only 10-

year protection. School BCG appears to be cost-effective for the 'low-risk' population only if their 10–15-year risk is very high: approximately 0.13–0.15%. This compares with current estimates of 0.03% (age 15–24) or 0.05% (age 15–29) (see Table 37).

Table 37: Cost-effectivensss of school BCG for low-risk group only by baseline risk of TB

Risk of TB over period of BCG protection (%)	10-year protection			15-year protection		
	Additional cost (£K)	QALYs gained	ICER (£/QALY)	Additional cost (£K)	QALYs gained	ICER (£/QALY)
0.03	718	1	767,800	720	1	696,100
0.05	671	3	193,500	674	4	185,300
0.07	625	6	104,100	629	6	100,700
0.09	578	9	67,700	583	9	65,900
0.11	532	11	48,000	538	11	46,900
0.13	485	14	35,700	492	14	35,000
0.15	439	16	27,200	447	17	26,800
0.17	392	19	21,000	401	19	20,800
0.19	346	21	16,300	355	22	16,300

Cost-effectiveness of school BCG as a catch-up for unvaccinated high-risk children

Based on the assumptions that 64% of high-risk children have been previously vaccinated, that they have a relative risk of 40 (compared with the low-risk group), and that BCG offers protection for 10 years, the schools programme appears to be cost-effective for areas with around 25–30% or more children in the high-risk group. If we assume 15-year BCG protection, school BCG appears cost-effective with around 10–15% or more in the high-risk group (see Table 38).

Table 38: Cost-effectiveness of school BCG by percentage of cohort in high-risk group

'High-risk' as % of cohort	10-year protection			15-year protection		
	Additional cost (£K)	QALYs gained	ICER (£/QALY)	Additional cost (£K)	QALYs gained	ICER (£/QALY)
0	718	1	767,800	674	4	185,300
5	646	4	180,700	573	8	70,800
10	574	6	92,400	471	13	37,600
15	502	9	56,700	370	17	21,700
20	430	11	37,400	268	21	12,500
25	358	14	25,300	167	26	6,400
30	286	17	17,100	65	30	2,200

These results are sensitive to the estimated mean cost of treatment and QALY loss per case of TB age 15–24/29.

11.3.6 From evidence to recommendations

The GDG noted that the schools BCG programme was for those at low risk of TB and previously unvaccinated, whilst those at higher risk of TB (see section 10.2) receive BCG vaccination either at birth or on entry to the UK.

Whilst BCG in school-age children has a protective efficacy of 75–80% lasting 10–15 years, the incidence of active TB in those at low risk is now in the order of 1 case per 100,000, with a continuing downward trend.

England and Wales meet the accepted international criteria for the cessation of universal BCG vaccination in a low-prevalence country,{291} and have done so at least since 2000.

Economic modelling shows that the schools programme is not cost effective, and extremely expensive with an incremental cost-effectiveness ratio between £696,000 and £767,000 for low-risk individuals.

The schools programme becomes cost-effective only if 15% or more of the children included are at higher risk and previously unvaccinated.

For these reasons, it was felt that routine BCG vaccination of children aged 10 to 15 in schools should not continue. Those children at risk will either have been vaccinated neonatally (see section 11.2) or on entry to the UK (see section 11.4). Where universal childhood screening and vaccination is thought appropriate for an area because of very high local incidence, then this would be better achieved by a local universal neonatal BCG policy.

11.3.7 RECOMMENDATIONS

R94 Routine BCG vaccination is not recommended for children aged 10–14.

- Healthcare professionals should opportunistically identify unvaccinated children older than four weeks and younger than 16 years at increased risk of TB (see section 10.2) who would have qualified for neonatal BCG and provide Mantoux testing and BCG (if Mantoux negative). C

2006

- This opportunistic vaccination should be in line with the Chief Medical Officer's advice on vaccinating this age group following the end of the school-based programme[20]. D(GPP)

R95 Mantoux testing should not be done routinely before BCG vaccination in children younger than six years unless they have a history of residence or prolonged stay (more than one month) in a country with a high incidence of TB[21]. D(GPP)

11.4 For new entrants from high-incidence countries

11.4.1 Clinical introduction

The incidence of tuberculosis in new entrants from countries of high incidence (40/100,000 per year or greater) is high, peaking 2–3 years after first entry, and falling significantly after 10 years, but remaining well above general UK population rates (see Appendix G). Up to 30% of such recent arrivals from the Indian subcontinent are tuberculin negative.{296},{297} Since they will be living in communities with a rate of TB some 25 times that of the white UK-born community, they may benefit from BCG vaccination to reduce the risk of acquiring TB disease. Such a BCG policy would however have to take into account the possibility of false negative Mantoux test from HIV co-infection.

11.4.2 Current practice

In the Department of Health's *Immunisation against infectious diseases* (the Green Book) 1996,{3} the following recommendation is made for new entrants from countries with a high prevalence of tuberculosis, their children and infants wherever born.

'*New entrants to the UK,* including students, from countries with a high prevalence of tuberculosis, and all refugees and asylum seekers, should be tuberculin tested as part of the initial screening procedure unless there is **definite** evidence of a BCG scar. Those with positive reactions should be referred for investigation as they may

[20] Available from www.dh.gov.uk
[21] More than 40 cases per 100,000 per year, as listed by the Health Protection Agency (go to www.hpa.org.uk and search for 'TB WHO country data').

require chemoprophylaxis or treatment. BCG immunisation should be offered immediately to those who are tuberculin negative.'

Under section 32.4.1d of the same document HIV-positive individuals are listed as one of the contraindicated groups to whom BCG vaccine should not be given with the following comment:

'BCG is absolutely contraindicated in symptomatic HIV positive individuals. In countries such as the UK where the risk of tuberculosis is low, it is recommended that BCG is withheld from **all** subjects known or suspected to be HIV positive, including infants born to HIV positive mothers. There is no need to screen mothers for HIV before giving BCG as part of a selective neonatal immunisation programme (see 32.3.2(e))'.

The newly updated chapter of the draft 2006 Green Book{21} states:

'BCG immunisation should be offered to... previously unvaccinated, tuberculin-negative new entrants under 16 years of age who were born in or who have lived for a prolonged period (at least three months) in a country with an annual TB incidence of 40/100,000 or greater.'

Readers should also be aware of the recommendations made for neonates (see section 11.2).

11.4.3 Methodological introduction

Studies investigating the effectiveness of BCG vaccination in new entrants from high-risk countries in preventing TB infection or disease were targeted. No systematic reviews, randomised controlled trials, cohort or case control studies were found that directly addressed the area.

One meta-analysis conducted in the USA{298} demonstrated that BCG vaccine had protective efficacy across a wide range of study conditions, BCG strains, populations, age ranges and vaccine preparation methods. BCG efficacy in new entrants from countries with a high TB incidence was not addressed.

Since the meta-analysis did not use cross-design analysis, it was appropriate to grade evidence statements according to whether they were derived from the RCT (level 1), clinically controlled trial (level 2) or case control study (level 2) results.

Factors for consideration raised by the meta-analysis included:

- differences in the characteristics and methodological quality of individual studies were addressed by a sensitivity analysis, expressed as a study quality validity score
- among 13 prospective trials, study validity explained 30% of the between-study variance in the trials, and geographical latitude accounted for 41% of the variance
- among the 10 case-control studies, data validity score was the only variable to explain a substantial amount (36%) of the heterogeneity
- different strains of BCG were not associated with more or less favourable results in the 13 trials, as differing BCG strains administered in the same populations provided similar levels of protection.

One non-analytic study from the UK{299} was excluded due to methodological limitations presented in Appendix I.

11.4.4 Evidence statements

Evidence was found for the efficacy of BCG vaccination in preventing:

- pulmonary TB disease
- TB deaths
- TB meningitis
- disseminated TB.

Evidence for these four outcomes is presented in Table 39.

Table 39: Summary of evidence: BCG vaccination for new entrants

Outcomes	**Intervention: BCG vaccinated *vs.* unvaccinated infants**	**Results**	**Association/statistical significance**	**Ref and NICE grade**
Pulmonary TB disease	Seven RCTs	Protective effect 0.63	Combined RR 0.37 (95% CI 0.18 to 0.74)	{298} 1+
	Six clinically	Protective	Combined RR 0.49 (95%	{298}

	controlled trials	effect 0.51	CI 0.34 to 0.70)	2+
	Ten case control studies	Protective effect 0.50	Combined OR 0.50 (95% CI 0.39 to 0.64)	{298} 2+
TB deaths	Three RCTs and four clinically controlled trials	Protective effect 0.71	Combined RR 0.29 (95% CI 0.16 to 0.53)	{298} 2+
TB meningitis	Five case control studies	Protective effect 0.64 (based on 181 cases of TB meningitis)	Combined OR 0.36 (95% CI 0.18 to 0.70)	{298} 2+
Disseminated TB	Three case control studies	Protective effect 0.78	Combined OR 0.22 (95% CI 0.12 to 0.42)	{298} 2+

11.4.5 From evidence to recommendations

The GDG noted that there was little data in this field. The high rates of tuberculosis in recently arrived new immigrants from high incidence countries was also noted from epidemiological data over the last 25 years.

Although there is no direct evidence in this group in the UK, the meta-analysis cited above was regarded as applicable.

Analysis of the evidence on BCG efficacy has shown no evidence for persons aged over 35. The GDG felt that for this pragmatic reason, BCG vaccination should be limited to those under 36, unless they have occupational risk factors.

11.4.6 RECOMMENDATIONS

Readers should also be aware of the recommendations under new entrant screening (section 12.8). This process should include Mantoux tests on appropriate new entrants and risk assessment for HIV prior to vaccination.

R96 BCG vaccination should be offered to Mantoux-negative new entrants[22] who:

- are from high-incidence countries, *and*
- are previously unvaccinated (that is, without adequate documentation or a characteristic scar), *and* B
- are aged:
    - younger than 16 years, **D(GPP)** or

2006

[22] People who have recently arrived in or returned to the UK from high-incidence countries.

- 16 to 35 years[23] from sub-Saharan Africa or a country with a TB incidence of 500 per 100,000.

11.5 For healthcare workers

11.5.1 Clinical introduction

Although earlier studies had not shown an association, in the 1990s healthcare workers were shown to have twice the expected incidence of TB, allowing for age, sex and ethnic factors.{300} Because of the risk of exposure, it became standard practice to recommend BCG vaccination to people commencing healthcare work who would have contact with patients or clinical material, if they had not had prior BCG vaccination, and were Mantoux test negative.

11.5.2 Current practice

In *Immunisation against infectious disease* (the Green Book),{3} the Department of Health recommended BCG vaccination for all those at *higher risk of tuberculosis.* Under section 32.3.2a this included:

'**Health service staff** who may have contact with infectious patients or their specimens. These comprise doctors, nurses, physiotherapists, radiographers, occupational therapists, technical staff in microbiology and pathology departments including attendants in autopsy rooms, students in all these disciplines, and any others considered to be at high risk. It is particularly important to test and immunise staff working within maternity and paediatric departments, and departments in which patients are likely to be immunocompromised, eg transplant, oncology and HIV units.'

The newly updated chapter of the draft 2006 'Green book'{21} states:

'People in the following occupational groups are more likely than the general population to come into contact with someone with TB:

- healthcare workers who will have contact with patients or clinical materials

[23] The draft 2006 Green Book recommends BCG for new entrants only up to the age of 16. However in this guideline BCG is recommended for those up to 35 years who come from the countries with the very highest rates of TB because there is some evidence of cost-effectiveness.

- laboratory staff who will have contact with patients, clinical materials or derived isolates...'

11.5.3 Methodological introduction

Studies investigating the efficacy of BCG vaccination in health care workers for preventing the development of TB infection or disease in comparison to unvaccinated healthcare workers were targeted. One systematic review was found that addressed the topic.

One systematic review conducted in the USA{301} included two randomised controlled trials, two prospective cohort studies, one historically controlled study, one retrospective cohort study and six non-analytic studies. Information on the study methods and results was reported for only four of the six non-analytic studies. The scope was international, but all 12 studies were conducted in the northern hemisphere, 10 in temperate zones situated far from the equator, the eleventh in California, and for the twelfth, the specific setting was unknown.

The systematic review was methodologically sound, and hence it could technically be given a grading of 1+. However, the review did not conduct a meta-analysis due to the heterogeneity of study designs and methodological limitations in each of the studies. The methodological limitations of individual studies contained within the review meant that there was insufficient robust data from which to derive evidence statements for this area. The review authors noted that despite methodological limitations, all six controlled studies reported a protective effect for BCG vaccination.

11.5.4 From evidence to recommendations

Whilst the systematic review was sound, all of the studies had multiple methodological flaws. There was however a consistent trend to benefit in the six controlled studies. Also, given the weight of evidence for the efficacy of BCG in other settings, it seemed unlikely that BCG would not be effective in this population. The GDG also noted that potential TB exposure continues throughout a career in individuals with patient or clinical material contact, and is not age limited.

There is not sufficient age-specific evidence to make recommendations on BCG vaccination for people over 35 but vaccination is recommended for healthcare

workers of all ages because of the increased risk to them – and consequently the patients they care for – if they remain unvaccinated.

11.5.5 RECOMMENDATIONS

R97 BCG vaccination should be offered to healthcare workers, irrespective of age[24], who: D(GPP)

- are previously unvaccinated (that is, without adequate documentation or a characteristic scar), *and*
- will have contact with patients or clinical materials, *and*
- are Mantoux (or interferon-gamma) negative.

Cross-referring:

For details of occupational health screening, see sections 13.1 and 13.2

11.6 BCG vaccination for contacts of people with active tuberculosis

11.6.1 Clinical introduction

Contacts of cases of pulmonary tuberculosis are at risk of contracting TB. This is particularly the case with household or close contacts of sputum smear-positive disease, where up to 10% become infected (see section 12.2). It may take several weeks to develop an immune response to infection, as judged by a positive tuberculin skin test. A second Mantoux test has to be performed in those whose initial test is negative, six weeks after the initial negative one and a decision made with the second result.{6} Those with serial negative skin tests are deemed not to have been infected, but BCG vaccination up to and including the age of 35 years is recommended. The index case should be rendered non-infectious within a few weeks by anti-tuberculosis drug treatment, but tuberculin-negative contacts remain at risk if there are secondary cases.

2006

[24] As outlined in the Green Book, there is not sufficient age-specific evidence to make recommendations on BCG vaccination for people older than 35 (see full guideline for details). However, in this guideline BCG vaccination is recommended for healthcare workers of all ages because of the increased risk to them – and consequently the patients they care for – if they remain unvaccinated.

11.6.2 Current practice

The Department of Health's *Immunisation against infectious disease* (the Green Book) 1996{3} recommended BCG vaccination for all those at *higher risk of tuberculosis*.{3} Under section 32.2d this included:

'**Contacts** of cases known to be suffering from active pulmonary tuberculosis. Contacts of a sputum smear positive index case may have a negative tuberculin skin test when first seen but be in the early stages of infection before tuberculin sensitivity has developed. A further skin test should be performed six weeks later and immunisation only carried out if this second test is negative. (If the second skin test is positive, the patient has converted and must be referred for consideration of chemoprophylaxis). However, if for some reason a further test is impossible, vaccine may be given after the first test. Newly born babies should be given prophylactic isoniazid chemotherapy and tuberculin tested after three to six months. If the skin test is positive, chemoprophylaxis is continued; if negative, BCG vaccine is given provided the infant is no longer in contact with infectious tuberculosis. Newly born contacts of other cases should be immunised immediately.'

The newly updated chapter of the draft 2006 Green Book{21} states:

'BCG immunisation should be offered to... previously unvaccinated tuberculin-negative contacts of cases of respiratory TB (following recommended contact management advice – currently Joint Tuberculosis Committee of the British Thoracic Society 2000 [{6}] and National Institute for Health and Clinical Excellence 2006 [this document]...'

11.6.3 Methodological introduction

The focus was on studies investigating the efficacy of BCG vaccination in contacts of those with diagnosed active tuberculosis disease in comparison to unvaccinated contacts from the same population. One cohort study and five non-analytic studies were identified. All studies addressed BCG vaccination of contacts prior to their exposure to the index case.

One prospective cohort study conducted in South Korea{302} over a period of approximately two and a half years reported on the protective efficacy of BCG

2006

vaccination against TB disease in child contacts. Four studies{278},{303},{304},{305} reported contact tracing results that included stratification of contacts by BCG vaccination status. BCG vaccination status was not the primary variable used to generate group allocation or to stratify the analysis of the results, and for this reason the studies were classified as non-analytic. One study was conducted in the UK (England, Wales and Scotland) and two studies in Scotland. A fourth study conducted in Brazil dealt with contacts of index cases diagnosed with MDR TB. Although the latitude effect could have influenced the study findings, the study was included since it focused on BCG vaccination in a contact population at risk of acquiring MDR TB disease. MDR TB is not addressed in the three UK-based studies.

A fifth non-analytic study was excluded due to methodological limitations, which are presented in the appendix I.

11.6.4 Evidence statements

Evidence on the efficacy of BCG vaccination in preventing TB disease was found for contacts:

- of index cases
- of index cases diagnosed with MDR TB
- belonging to different ethnic groups

The evidence is presented in Table 40.

Table 40: Summary of evidence: BCG vaccination for contacts of people with TB

Population	Results N (%) TB disease cases in BCG- vaccinated versus unvaccinated persons	Association/statistical significance	Ref and NICE grade
Contacts of index cases	Child contacts aged 0–5: protective effect 0.70; 46/806 (5.7) *vs.* 80/417 (19.2) scored six or higher, indicating TB disease	Not reported	{302} 2+
	Stratification by age: protective effect 0.74	Summary RR 0.26 (95%CI 0.62 to 0.82)	{302} 2+
	Close contacts: 14/1081 (1.3) *vs*. 149/3587 (4.2)	Not reported	{278} 3+
	Contacts: 16/1821 (0.88) *vs.* 62/3595 (1.72)	Not reported	{303},{304} 3+
	Contacts with new TB (active TB disease plus those on	p<0.001	{303},{304} 3+

	treatment for latent TB infection): protective effect 0.62; (1.15) *vs.* (3.06)		
	Contacts: 14/1605 (0.87) *vs*. 34/1761 (1.93)	Not reported	{303},{304} 3+
	Contacts received chemotherapy/treatment for latent TB infection for TB disease/infection: protective effect 0.59; 23/1605 (1.4) *vs.* 60/1761 (3.4)	Not reported	{303},{304} 3+
Contacts of index cases diagnosed with MDR TB	Protective effect 0.69 (excluding three contact TB cases with drug-susceptible isolates); 8/153 (5) *vs.* 9/65 (14)	RR 0.35 (95%CI 0.13 to 0.99, p< 0.05)	{305} 3+
	TB disease found significantly more in unvaccinated MDR TB contacts	RR 3.1 (95%CI 1.2 to 8.1)	{305} 3+
Contacts belonging to different ethnic groups	Asian contacts: 7/425 (1.6) *vs.* 57/1479 (3.9)	Not reported	{278} 3+
	Non-Asian (mainly white) contacts: 7/656 (1.1) *vs.* 92/2108 (4.4)	Not reported	{278} 3+
	Asian contacts: 0/86 *vs.* 5/228 (2.19)	Not reported	{303},{304} 3+
	Non-Asian (mainly white) contacts: 16/1735 (0.92) *vs.* 57/3367 (1.69)	Not reported	{303},{304} 3+
	Incidence of TB in black African *vs.* white contacts: 2.2 versus 0.4 per 1,000 person-years	p<0.001[25]	{305} 3+

2006

11.6.5 From evidence to recommendations

The appraised evidence shows some protective efficacy for BCG vaccination given before contact with tuberculosis, but none of the studies addressed the efficacy of BCG administered to tuberculin-negative contacts after exposure to TB. However, such individuals may be at increased risk from secondary TB cases if not vaccinated. As for new entrants, the potential benefit of BCG vaccination is reduced with age, and there is no reason to change the upper age limit of 35 years, which is currently widely used.

RECOMMENDATION

R98 BCG vaccination should be offered to Mantoux-negative contacts of people with respiratory TB (see section 12.2 for details of contact tracing) if they are

[25] Using Cox's regression test, ethnicity was no longer associated with incidence of TB disease.

previously unvaccinated (that is, without adequate documentation or a characteristic scar) and are: D(GPP)

- aged 35 or younger
- aged 36 and older and a healthcare or laboratory worker who has contact with patients or clinical materials (see section 11.5).

Cross-referring:

For details of contact tracing, see sections 12.2–12.6.

11.7 Other groups

The Department of Health currently recommends BCG vaccination for a range of other people who may be at risk from TB.{21} This guideline concentrated on the groups given individually above but for completeness this section addresses the other groups at risk, who stand to benefit from BCG vaccination. For veterinary surgeons, abattoir workers and other people working with animals, there are a number of possible sources of infection, but no standard occupational health screening. Workplace screening is likely to be provided by private sector firms, and is therefore outside the remit of NICE. However, a number of regulations apply:

- the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995, which require employers to notify the Health and Safety Executive
- the Management of Health and Safety at Work Regulations 1999, which require general standards of risk assessment
- the Control of Substances Hazardous to Health Regulations 2002, which require employers to assess infection risk and prevent or control exposure.

11.7.1 RECOMMENDATION

R99 BCG vaccination should be offered to previously unvaccinated, Mantoux-negative people aged35 or younger in the following groups at increased risk of exposure to TB, in accordance with the 'Green Book':{21}D(GPP)

- veterinary and other staff such as abattoir workers who handle animal species known to be susceptible to TB, such as simians
- prison staff working directly with prisoners
- staff of care homes for elderly people

- staff of hostels for homeless people and facilities accommodating refugees and asylum seekers
- people going to live or work with local people for more than 1 month in a high-incidence country.[26]

See section 11.5 for advice on healthcare workers.

12 Active case finding

12.1 Overview

12.1.1 Clinical introduction

Active case finding is looking systematically for cases of active tuberculosis and latent infection in groups known, or thought to be, at higher risk of tuberculosis, rather than waiting for people to develop symptoms/signs of active disease and present themselves for medical attention (passive case finding). Active case finding is informed by a knowledge of the general epidemiology of TB in the country, and in population subgroups. The current incidence of active TB in England and Wales is 12.9 cases per 100,000 population per year, with individual ethnic groups having rates of 4 per 100,000 (white), 104 per 100,000 (Indian), 145 per 100,000 (Pakistani), and 211 per 100,000 (black African).{140} Data are not available on latent tuberculosis rates in the general population. Active case finding, if targeted on appropriate groups, or subgroups, should have a yield substantially above that that would be found by chance screening. The Chief Medical Officer's TB Action Plan{2} set improvements in case finding as one of the essential activities to improve TB care in England and Wales, and to reverse the trend of increasing incidence.

12.1.2 Current practice

The review of current services included service provision and organisation for active case finding in terms of contact tracing (sections 12.2 and 12.3), new entrant screening (section 11.7), and screening other risk groups.

Outside London, 25% of service providers had some screening for high-risk groups, whereas within London, 39% had such screening. Examples of high-risk groups were drug users, the homeless and alcoholics.

[26] Go to **www.hpa.org.uk** and search for 'WHO country data TB'.

12.2 Contact tracing: human-to-human transmission

12.2.1 Clinical introduction

Contact tracing and examination have traditionally been undertaken to find associated cases, to detect people infected but without evidence of disease (latent infection) and to identify those not infected and for whom BCG vaccination may be appropriate. Where recent infection has occurred (eg clinical disease in children), contact tracing is done to find a source of infection, and any co-primary cases. In people with latent tuberculosis, BCG vaccination does not prevent its development into active disease. BCG vaccination is addressed in chapter 10 of this guideline.

Five contact studies in England and Wales,{306–310} reporting 22,971 contacts in the early 1990s, showed that up to 10% of new TB cases were diagnosed through contact tracing, that disease occurred in about 1% of contacts, and that disease was usually found on the first visit in unvaccinated contacts of sputum smear-positive disease. Three smaller studies reported in the late 1990s in England and Wales,{311–313} largely confined to close contacts, showed a mean number of contacts examined at 6.5 per index case, and confirmed a secondary case yield of 1% (1,000/100,000).

Smear-negative pulmonary tuberculosis is significantly less infectious than smear-positive, but some transmission does occur. Studies in San Francisco{314} and Western Canada{315} using DNA fingerprinting estimated this transmission risk (as a proportion of smear-positive transmission risk) at between 0.22 and 0.18–0.35 respectively, similar to estimates (0.28) using 'conventional' methods.{316} DNA fingerprinting studies may also identify clusters not identified by 'conventional' contact tracing and in some cases assumed to be recently linked.{314},{315}

12.2.2 Current practice

The review of current services found that outside London, 70% of service providers had contact clinics and 16% saw patients at home. Within London, 91% had a contact tracing clinic, and no service providers saw patients at home other than in exceptional cases.

An assessment of the extent of current contact tracing practice can be made by comparing the number of notified cases with the number of contacts screened. The graph below, where each dot represents a service provider, and clinics which only do tracing have been removed, shows that there is considerable variation in the number of contacts traced per index case. (Perfect consistency, which is an unreasonable expectation, would be demonstrated in a straight line.)

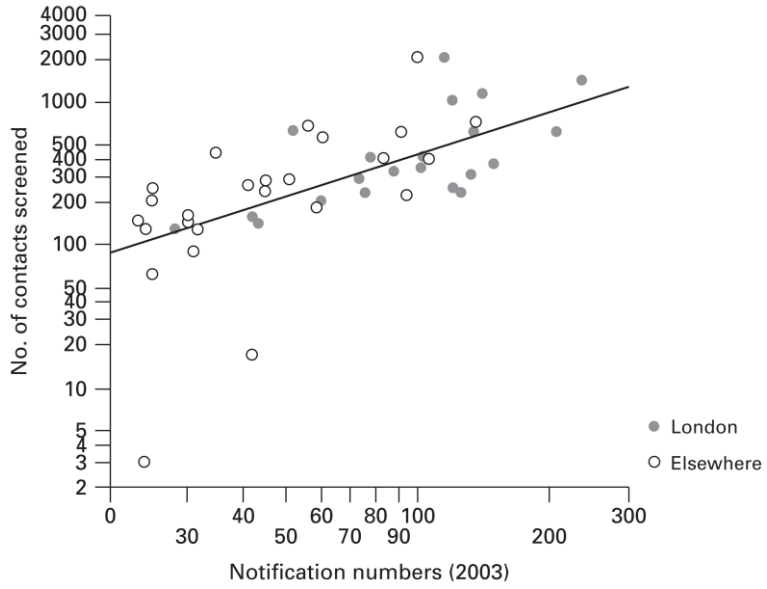

Figure 9 Correlation of contacts screened with cases notified (logarithmic scale)

A similar comparison has been made between the number of contacts traced and the number of treatments for latent TB infection cases, and is reported under section 10.1.

12.2.3 Methodological introduction

Two clinical questions were drawn up to search the evidence base for this topic. The results of the searches and the critical appraisal are discussed below for each in turn.

Are contact tracing procedures effective in identifying cases of tuberculosis disease or infection (excluding contacts of cattle with TB)?

No systematic reviews or randomised controlled trials were found that met the inclusion criteria for this question.

The literature search identified 10 studies conducted in England and Wales that reported epidemiological descriptions of specific contact tracing exercises. These

studies did not include comparative case yield data from other contact tracing or case finding exercises in similar populations and settings, and so were not considered for appraisal. Without comparative data, these studies could not evaluate the effectiveness of the specific contact tracing intervention method used. Nevertheless these studies contribute towards an epidemiological overview of contact tracing in England and Wales, and the main results of these studies are collated in Table 41 below in order to provide local background information on this aspect of active case finding.

Table 41: Descriptive studies of contact tracing carried out in England and Wales

Reference	Description	Results
Ruddy MC, Davies AP, Yates MD, Yates S *et al*. Outbreak of isoniazid resistant tuberculosis in north London. *Thorax* 2004;**59(4)**:279–285.	Study type: descriptive. Population: contact tracing of isoniazid resistant TB outbreak in North London, including prisons. Study period: retrospective analysis 1995–2001.	• At least 440 named close contacts of confirmed or probable TB cases to date. • Screening of 269 close contacts yielded 13 confirmed or probable TB cases, 13 clinical cases, and three linked cases. • This represents a transmission rate of 11% among close contacts screened to date. • 27 infected contacts were placed on treatment for latent TB infection.
Corless JA, Stockton PA, Davies PD. Mycobacterial culture results of smear-positive patients with suspected pulmonary tuberculosis in Liverpool. *European Respiratory Journal* 2000;**16**:976–979.	Study type: descriptive. Population: contact tracing of suspected pulmonary TB from two hospitals in Liverpool. Study period: retrospective analysis 1996–1999.	• A total of 937 contacts were identified from 57 index patients with cultured *M. tuberculosis*. • No contact in the study developed tuberculosis while under surveillance.
Ansari S, Thomas S, Campbell IA, Furness L, Evans MR. Refined tuberculosis contact tracing in a low incidence area. *Respiratory Medicine* 1998;**92(9)**:1127–1131.	Study type: descriptive. Population: patients with TB and their contacts in South Glamorgan. Study period: retrospective analysis 1992–1994.	• A total of 726 contacts were identified from 103 index patients, with 707 contacts receiving full screening. • TB disease was found in 7 (1%) close contacts, all identified

		at the initial screening (one with smear-positive index case; five with two overseas index cases with unknown smear status; one with child index case with unknown smear status). • TB disease was found later in a further five contacts initially screened and cleared (in two cases the protocol was not followed correctly and three cases developed extra- pulmonary TB. • Treatment for latent TB infection was given to 21 (2.9%) of close contacts.	2006
Irish C, Jolly E, Baker T. Contact tracing smear positive and non-pulmonary tuberculosis in a high incidence area. *Thorax* 1997;**52**:A34.	Study type: descriptive epidemiological study. Population: contacts of non-pulmonary (NP), sputum smear-positive (POS), and negative (NEG) cases of tuberculosis disease in Tower Hamlets. Study period: 1995.	• One of 158 (0.5%) contacts of POS cases, four of 196 (2%) contacts of NEG cases, and none of 57 contacts of NP cases were treated for tuberculosis disease. • Twenty-two of 158 (14%) POS contacts, 21 of 196 (11%) NEG contacts, and five of 57 (9%) NP contacts received treatment for latent TB infection. • Differences in proportions of POS, NEG, and NP contacts requiring one or more repeat X-ray, further clinic follow-up, treatment for latent TB infection or full tuberculosis treatment were not significant.	
Stoddart H, Noah N. Usefulness of screening large numbers of contacts for tuberculosis: questionnaire-based review. *British Medical*	Study type: cross-sectional survey Population: 155 districts in England and Wales where in the preceding three years more than 100 contacts were screened in response to	• Forty-four cases of tuberculosis disease were found in 18 of the 56 investigations, giving a detection rate of 0.375%.	

Journal 1997;**315**:651.	specific incidents. Study period: April 1994.	• A further 106 (0.9%) contacts received treatment for latent TB infection. • The development of tuberculosis in 39 investigations with details available was significantly correlated with the proportion of contacts who had tuberculin skin test positive results (P=0.008).
Harding MJ, Pilkington P, Thomas J. Tuberculosis epidemiology in Croydon. *Public Health* 1995;**109**:251–7.	Study type: descriptive. Population: contact tracing in response to tuberculosis incidents in Croydon. Study period: retrospective analysis 1988–1991.	• A total of 522 close contacts were identified from 172 index cases. • Three cases of tuberculosis were identified from the contacts (0.6%). • Forty-eight contacts (9.2%) had either a positive Heaf test or chest X-ray indicative of past primary infection. • 19.6% of contacts of index patients with smear-positive disease were 'positive' *vs.* 9.8% of contacts of non-smear positive index patients, *vs.* 5.2% of patients with non-pulmonary disease (P=0.0002).
Hardinge FM, Black M, Chamberlain P. TB contact tracing in South Buckinghamshire from 1994 to mid 1998. *Am J Respir Crit Care Med* 1999;**159**:A303.	Study type: descriptive. Population: all patients with TB and their contacts in South Buckinghamshire. Study period: retrospective analysis 1994 to mid 1998.	• 369 contacts were identified from 72 index cases. • Eight cases of TB were identified among contacts, four at initial screening (1%) – all were close contacts of smear-positive pulmonary disease index cases. • Three contacts were given treatment for latent TB infection (0.8%), and 143 (38%)

2006

		were given BCG vaccination.
Ormerod LP. Results of tuberculosis contact tracing: Blackburn 1982–90. *Respiratory Medicine.* 1993;**87**:127–131.	Study type: descriptive. Population. contact tracing in Blackburn using methods 'virtually identical' to procedures recommended in 1983 by the JTC. Study period: retrospective analysis 1982–1990.	• 7,017 close contacts were identified from 649 index cases. • 50 cases of TB (0.7% of all contacts) were identified, 13 in the white ethnic group, and 37 in the Asian ethnic group. • 38% of cases in the Indian subcontinent ethnic group were contacts of smear-positive pulmonary disease, and 46% were contacts of other forms of respiratory disease. • All cases of TB were in white contacts of index cases with smear-positive pulmonary disease.
Kumar S, Innes JA, Skinner C. Yield from tuberculosis contact tracing in Birmingham. *Thorax* 1992;**47**:875.	Study type: descriptive. Population: yield from contact tracing of notified TB cases at the Birmingham chest clinic using a contact tracing procedure 'broadly similar' to 1990 BTS guidelines. Study period: retrospective analysis 1987–1989.	• 7,960 contacts were identified from 788 index cases. • 75 new cases of TB were identified from contacts (1% of all contacts), 46 of Indian subcontinent origin, 15 white, and 14 black Caribbean. • 254 contacts were given treatment for latent TB infection (3% of all contacts). • All contacts with TB disease were contacts of index cases with pulmonary smear-positive TB except for six (8% of total) Indian contacts of index cases with non-respiratory disease.
Hussain SF, Watura R, Cashman B, Campbell IA, Evans MR. Audit of a tuberculosis contact	Study type: descriptive. Population: TB contact tracing in South Glamorgan. All patients with a diagnosis of	• 611 contacts were identified from 101 index patients. • Active TB disease was

2006

tracing clinic. *BMJ.* 1992;**304**:1213–15.	active TB disease who appeared in the contact tracing records and laboratory data from the Public Health Laboratory Service (PHLS) *Mycobacterium* Reference Unit within this period were included in the study, as were all recorded contacts of these patients. Study period: retrospective analysis 1987–89.	diagnosed in five contacts (two of Indian subcontinent origin, three of other origins), all made on initial screening. All were close contacts and none were known to have been vaccinated. • Four contacts who received treatment for latent TB infection were also close contacts of patients with smear-positive pulmonary TB and had not been vaccinated.
Teale C, Cundall DB, Pearson SB. Time of development of tuberculosis in contacts. *Respiratory Medicine* 1991;**85**:475–7.	Study type: descriptive. Population: contact tracing procedures at the Leeds chest clinic Study period: retrospective analysis 1983–1987.	• 6,602 contacts were identified from 555 notified index cases. • 42 (8%) contacts had TB disease (10 cases smear or culture positive, five contacts of Asian origin, five contacts of non-family members; four cases diagnosed more than one year after first clinic attendance). • 35 (6%) previously unimmunized child contacts with Heaf grade 2 or more results received treatment for latent TB infection.

Of the 17 studies appraised, 11 were excluded due to methodological limitations, which are presented in Appendix I. Six non-analytic studies were included as evidence in two main areas:

- non-homeless and homeless populations
- contact tracing and DNA fingerprinting analysis.

Are contact tracing procedures which identify casual contacts in addition to close contacts effective in identifying cases of tuberculosis disease or infection?

Studies were included that compared the number of cases of latent tuberculosis infection and/or active tuberculosis disease identified during contact tracing in

groups of close and casual contacts. No systematic reviews, randomised controlled trials, cohort or case control studies were found that met the inclusion criteria for this question.

Seven studies on contact tracing in close and casual contacts were identified, but six of these{316–321} were excluded due to methodological limitations presented in Appendix I. One prospective non-analytic study {322} was included as level 3 evidence for this question.

12.2.4 Evidence statements

Contact tracing compared in non-homeless and homeless populations

A study carried out in the USA{323} found that contact tracing identified significantly more contacts in non-homeless compared to homeless tuberculosis cases. The evidence is presented in Table 42.

Table 42: Summary of evidence: contact tracing in homeless and non-homeless people

Outcome	Results Homeless *vs.* non-homeless TB index cases	Statistical significance	NICE grade
Mean number contacts identified	2.7 *vs.* 4.8	p<0.001	3+
Four plus contacts identified	40 (26) *vs.* 1419 (50)	p<0.0001	3+
No contacts identified N (%)	70 (46) *vs.* 304 (11)	p<0.0001	3+

Contact tracing and DNA fingerprint analysis

Five non-analytic studies compared DNA fingerprint analysis of transmission links between cases of tuberculosis with the number of epidemiological links established through contact tracing for the same set of cases. These studies did not have a control group. Factors for consideration within this topic are used below.

- DNA fingerprint analysis can only be carried out on culture-positive cases of *M. tuberculosis*. Contact tracing includes culture-positive and-negative cases, and identifies cases of latent infection. Contact tracing therefore covers a wider population of at-risk contacts than DNA fingerprinting analysis, so the procedures are not equivalent comparators.

- Reliance on *M. tuberculosis* isolates means that molecular typing usually occurs some time after contact tracing has commenced, and so cannot complement in real time the epidemiological links established by the latter.
- None of the studies were carried out in the United Kingdom.
- Contact tracing was generally poorly reported and differed within each study setting.

Four studies{324–327} found that when contact tracing and DNA fingerprint analysis were carried out on the same group of contacts, tracing found fewer transmission links between identified cases of active tuberculosis than DNA fingerprint analysis. The evidence from the studies is presented in Table 43 below.

Table 43: Summary of evidence: DNA fingerprinting

Results: DNA fingerprint analysis	Results: Contact tracing	Ref and NICE grade
155 clustered TB cases	Identified links in 37/155 (24%) clustered cases; missed detectable links in 10/155 (6%) clustered cases; non-detectable (by contact tracing) links in 106/155 (68%) clustered cases.	{324} 3+
Four clusters of TB cases with transmission links identified	Identified links in 3/4 (75%) clusters.	{325} 3+
84 TB cases in 26 clusters	Identified links in 20/84 (24%) linked TB cases.	{326} 3+
96 TB cases in eight clusters	Two TB cases identified an unspecified number of cases in the same cluster as 'contacts'.	{327} 3+

One study{328} found that DNA fingerprint analysis identified erroneous transmission links inferred by contact tracing to exist between cases of tuberculosis disease.

Eight of 13 epidemiological transmission links (61.5%) identified by contact tracing were verified by DNA fingerprint analysis, but the remaining five (38.5%) cases linked by contact tracing did not acquire their infection from the putative source. (**3+**)

Close contacts compared to casual contacts in detecting latent tuberculosis infection

One study{322} found that both latent tuberculous infection and active tuberculous case yields were significantly higher for close compared to casual contacts of 302

index cases diagnosed at a single non-hospital practice. The evidence is summarised in Table 44 below.

Table 44: Summary of evidence: contact tracing in close and casual contacts

Outcomes	Close contacts N (%)	Casual contacts N (%)	Association/statistical significance (OR)	NICE grade
Latent TB infection	488 (55.9)	94 (26.4)	OR 3.54 (95%CI 2.68 to 4.69 p<0.00001)	3+
Active TB disease	40 (4.6)	2 (0.6)	OR 8.51 (95%CI 2.18 to 73 p<0.001)	3+

12.2.5 From evidence to recommendations

General issues

Contact tracing procedures should be carried out on a patient-centred basis. The GDG felt it was important to consider the lifestyle of an index/source case carefully as it may reveal places of close contact other than domestic or occupational such as homeless shelters, cinemas, bars, clubs, prisons or aircraft.{329}

Contact tracing is usually conducted according to the 'stone in the pond' principle,{330} and it is with this in mind that the recommendations below are set out. Closest contacts (those with most exposure, typically household contacts) are found and assessed first. If sufficient TB is found to raise clinical suspicion of further infection, another tier of contacts are traced, and so on. This helps to limit the effort put into such exercises.

Definition of close contacts

Descriptive studies from the UK which were considered by the GDG do not give a clear definition of close contacts and it is therefore difficult to give guidance on whom to trace.

It would be useful to give TB nurses an objective definition of close contacts, but there is insufficient evidence to make a recommendation on factors such as length of time spent in the same room without ventilation before 'close contact' is deemed to have occurred.

DNA fingerprint analysis

DNA 'fingerprint' analysis has been used to identify clusters that have not been identified by contact tracing. It can support the presumed links between cases.

Only one study checked the effectiveness of molecular typing through follow-up, and the GDG did not feel that the evidence base was sufficient to inform clinical recommendations.

Molecular typing will underestimate the epidemiological linkages relevant to contact tracing, because it relies exclusively on analysis of culture-positive TB isolates.

Who to include in contact tracing?

Whilst the highest pick-up will be in the contacts of pulmonary smear-positive cases, there is a significant yield from screening household contacts even of non-respiratory index cases, as this is assessing and screening a local population with a high incidence of TB.

Contacts with a cumulative total exposure to a smear positive case of TB exceeding eight hours within a restricted area equivalent to a domestic room are equivalent to domestic contacts; the guideline recommends tracing these contacts in addition to the domestic ones.

'Inform and advise' information is an important minimum level of TB education for all contacts once they are traced. However, for close contacts, this should not pre-empt screening and discussion with a healthcare professional (as a normal part of contact tracing), because of patient confidentiality.

12.2.6 RECOMMENDATIONS

R100 Once a person has been diagnosed with active TB, the diagnosing physician should inform relevant colleagues so that the need for contact tracing can be assessed without delay. Contact tracing should not be delayed until notification. D(GPP)

R101 Screening should be offered to the household contacts of any person with active TB, irrespective of the site of infection. Household contacts are defined as those who share a bedroom, kitchen, bathroom or sitting room with the index case. Screening should comprise: D(GPP)

- standard testing for latent TB for those aged 35 or younger, and consideration of BCG or treatment for latent TB infection once active TB has been ruled out

- interferon-gamma test six weeks after the Mantoux test, and consideration of BCG or treatment for latent TB infection once active TB has been ruled out, for those who:
  – are previously unvaccinated *and*
  – are household contacts of a person with sputum smear-positive TB *and*
  – are Mantoux negative (<6 mm)
- chest X-ray (if there are no contraindications) for those older than 35, possibly leading to further investigation for active TB.

2006

R102 For people with sputum smear-positive TB, other close contacts should be assessed. These may include boyfriends or girlfriends and frequent visitors to the home of the index case. Occasionally, a workplace associate may be judged to have had contact equivalent to that of household contacts, and should be assessed in the same way. D(GPP)

R103 Casual contacts of people with TB, who will include the great majority of workplace contacts, should not normally be assessed. C

R104 The need for tracing casual contacts of people with TB should be assessed if: D(GPP)

- the index case is judged to be particularly infectious (for example, evidenced by transmission to close contacts), *or*
- any casual contacts are known to possess features that put them at special risk of infection (See section 10.1).

R105 'Inform and advise' information should be offered to all contacts of people with smear-positive TB. D(GPP)

Cross-referring:

For details of diagnosing latent TB, see section 5.1.

For details of diagnosing active TB, see section 5.2.

For details of dealing with children aged less than 2 years who are close contacts of people with sputum smear-positive TB, see section 10.1.

For details of BCG vaccination, see section 11.6.

For examples of 'inform and advise' information, see Appendix H.

2006, amended 2011

This algorithm is currently being reviewed and has been temporarily removed.

2006, amended 2011

Figure 10 Algorithm for testing and treating asymptomatic children aged between 4 weeks and 2 years old who are contacts of people with sputum smear-positive TB

This algorithm is currently being reviewed and has been temporarily removed.

2006, amended 2011

Figure 11 Algorithm for asymptomatic household and other close contacts of all cases of active TB

12.3 Contact tracing: cattle-to-human transmission

2006

12.3.1 Clinical introduction

Tuberculosis in cattle, as judged by postmortem studies and tuberculin reactors, has become more common in England and Wales over the last 20 years. The highest rates in cattle are in the south west of England, parts of Wales and the West Midlands. Bovine tuberculosis is almost entirely caused by *M. bovis*, which can be differentiated from *M. tuberculosis* in the laboratory after culture. Following the increase in cattle TB, surveillance for human *M. bovis* infection was enhanced. However the reporting system of the PHLS (MycobNet, see chapter 13) reported only 210 humans with isolates of *M. bovis* between 1993–1997, approximately 1% of reported human *M. tuberculosis* complex isolates.{331} People with *M. bovis*

isolates were very different from those with other *M. tuberculosis* complex isolates. Of the 210, 200 were of white ethnic origin, with over three quarters aged 50 years or more, findings suggesting reactivation of disease acquired earlier in life.

The overwhelming majority of the UK population is at negligible risk from *M. bovis* infection because of milk pasteurisation. Continuing data from MycobNet since 1997{140} shows no increase in the numbers of human *M. bovis* isolates.

Readers should be aware of the Department of Health's advice on the public health implications of bovine TB.{332}

12.3.2 Current practice

The review of current services did not specifically ask for details, but some respondents supplied information on their work with bovine TB. It was regarded as being responsible for a significant workload in three HPU areas. Three clinics reported 28 cases of *M. bovis* infection, for which they had traced an average of six contacts per case. This would be a not insignificant workload for contact tracing services in a dispersed rural population.

12.3.3 Methodological introduction

No systematic reviews, randomised controlled trials, case control studies or non-analytic studies were found that met the inclusion criteria for this question. One cohort study{333} conducted in the USA was excluded due to methodological limitations listed in Appendix I. Two Canadian papers investigated human contacts of diseased elk, and one UK paper was purely descriptive of case yield but did not evaluate contact tracing as an intervention. There are therefore no evidence statements for this question.

12.3.4 From evidence to recommendations

Since there is little evidence of cattle–human or human–human transmission of *M. bovis* from national epidemiology or the limited UK data, the group considered that tuberculin skin testing and interferon-gamma testing should be limited to previously unvaccinated children and adolescents (age <16) who have regularly drunk unpasteurised milk from animals with udder lesions, with treatment for latent TB infection being offered to those with a positive result.

12.3.5 RECOMMENDATIONS

R106 'Inform and advise' information should be given to people in contact with TB-diseased animals. Diagnostic tests for latent TB should be considered only for children younger than 16 who have not had BCG vaccination and have regularly drunk unpasteurised milk from animals with TB udder lesions. D(GPP)

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see section 11.6.
For examples of 'inform and advise' information, see Appendix H.

12.4 Contact tracing: cases on aircraft

12.4.1 Clinical introduction

The evidence base upon which assessments can be made of the risks of transmission of TB in aircraft is relatively slim. The confined space and the recirculation of air clearly give rise to potential hazards. Whether or not these are greater for an individual on a single flight than, say, regular travel on the same commuter bus or train as an infectious case of TB cannot be established.

Aircraft passengers are, in theory at least, more readily identifiable than passengers of other kinds. Identifiability and traceability are not, however, synonymous and characteristically, aircraft passengers do not make multiple repeat journeys and are widely dispersed once they reach their destination. Further, airlines (who hold the passenger lists) may prove reluctant to disseminate information about the hazards of having travelled with them.

Recommendations about contact tracing where an aircraft passenger has been identified as having infectious TB must therefore be guided by the practicalities of the process.

12.4.2 Methodological introduction

Studies were targeted that attempted to establish whether latent tuberculosis infection and active tuberculosis disease identified by contact tracing in passenger

and crew contacts was due to recent transmission from an index case of tuberculosis on an aircraft. No systematic reviews, randomised controlled trials, or case control studies were found that met the inclusion criteria.

One cohort study conducted in the USA{334} compared case yields for latent tuberculosis infection identified by contact tracing in flight crew exposed to an index case of tuberculosis with flight crew with no prior exposure to infectious tuberculosis. Five non-analytic studies{335–339} were identified that investigated whether latent tuberculosis infection identified in passenger and crew contacts was due to prior risk factors for tuberculosis or recent exposure to an index case of tuberculosis on an aircraft. Methodologically, all six studies differed with regard to:

- varying geographical locations
- varying countries of residence of contacts
- differing exposure periods
- variation in prior BCG vaccination of contacts depending on country of residence
- sample sizes ranging from 100 to 760.

Prior risk factors for latent tuberculosis infection and contamination of tuberculin skin test results identified in the study populations included:

- high BCG vaccination rates
- prior exposure to family members or close friends with tuberculosis
- born or resident in a country with a high incidence of tuberculosis
- extensive travel in settings with a high incidence of tuberculosis
- having old, inactive tuberculosis
- exposure to tuberculosis in the workplace (excludes flight crew)
- exposure to other mycobacterial infection.

12.4.3 Evidence statements

Recent transmission of latent tuberculosis infection

One study {334} found significantly more cases of recent transmission of tuberculosis infection in aircraft crew exposed to an index case of tuberculosis than in a control group of non-exposed crew. Two studies{336},{337} found evidence of

recent transmission of TB infection in airplane contacts of cases with tuberculosis disease, while three other studies{335},{338},{339} found no conclusive evidence of recent transmission in airplane contacts of active TB disease cases. None of the studies reported symptoms of active tuberculosis in contacts. The evidence is presented in Tables 45 and 46 below.

Table 45: Exposed and non-exposed aircraft crew

N (%) exposure group Mantoux test positive	N (%) control group Mantoux test positive	Association/statistical significance	Ref and NICE grade
May–July 1993: 10/169; 5.9	**May–July 1993:** 13/247; 5.3	NS	{334} 2++
August–October 1993: 13/43; 30 (Mantoux test positive rates ≥5 mm induration)	**August–October 1993:** 13/247; 5.3 (Mantoux test positive rates ≥5 mm induration)	RR 5.74 (95%CI 2.86 to 11.54, p<0.01)	
11/43; 25.6 (Mantoux test positive of 10 mm induration)	4/247; 1.6 Mantoux test positive (rates of 10 mm induration)	RR 15.8 (95%CI rates 5.27 to 47.34, p<0.01)	

Table 46: Aircraft contacts with latent TB infection attributed to prior risk factors vs. aircraft-mediated transmission

N (%) Mantoux test positive contacts with prior risk factors for TB	N (%) Mantoux test positive contacts attributed to aircraft transmission	Ref and NICE grade
6/9 (66.6)	3/9 (33.3) Flight exposure-related conversion rate for latent TB infection was 1.3% (3/225 contacts)	{336} 3+
14/20 (70%)	6/20 (30) Flight exposure related conversion rate for latent TB infection was 0.8% (6/760 contacts)	{337} 3+
24/24 (100%)	0	{335} 3+
32/34 (94%)	2/34 (5.8) Impossible to determine whether two US-born Mantoux test positive reactors were due to aircraft transmission, since estimated 4–6% of the US population are Mantoux test positive	{338} 3+
5/5 (100%)	0	{339} 3+

Duration of exposure

One study{334} found that duration of exposure to the index case was the factor most strongly associated with latent tuberculosis infection among exposed aircraft crew contacts.

Over three months 49 (96%) crew contacts all had at least 14.5 total hours of exposure to the index case. Total time exposed to the index case during this period

was the variable most strongly associated with the probability of having a Mantoux test positive result (p<0.001) for all variables and interactions considered. (**2++**)

Seating proximity of infected contacts to the index case

One study (N=760){337} found a statistically significant relationship between Mantoux test -positive contacts with no prior risk factors for tuberculosis, and seating proximity to an index patient with MDR TB on an aircraft (RR 8.5, 95%CI 1.7 to 41.3, p=0.01). (**3+**)

Three studies (N=120,{338} N=100,{339} and N=225){336} found no evidence that Mantoux test -positive contacts without prior risk factors for tuberculosis were more likely to be seated in closer proximity to an index case with tuberculosis on an aircraft than Mantoux test -positive contacts with prior risk factors. (**3+**)

12.4.4 From evidence to recommendations

The evidence base for this topic is prone to publication bias, where reports of successful tracing are more likely to be of interest, and therefore the yield of these procedures is likely to be overestimated.

One of the studies{334} had a crew member as an index case and assessed transmission to other crew. This is therefore a workplace study and not directly applicable to passenger-to-passenger transmission.

The evidence base indicates low yield from aircraft-based contact tracing, but proximity to the index case was seen to be a risk factor. However, identifying proximity is costly and difficult. Seating records, or even passenger lists, are not always available, and the onus of contacting passengers lies with the airline. Similar possibilities for transmission arise in other forms of long-haul transport, but seating plans are not generally available in these situations.

'Inform and advise' information is of limited utility in such situations, where risk of infection is extremely low, neither the TB service nor the airline know which passengers are more susceptible to infection, and the passengers receiving such information will not be in contact with a TB service from whom they can seek further advice face to face.

It was therefore felt that it was not an effective use of resources to conduct contact tracing among aircraft passengers or similar transport scenarios, unless a seating plan was available, or where exceptional circumstances exist.

Such exceptional circumstances were identified as including: an index case with MDR TB, frequent coughing, and a flight of over eight hours' duration. The eight hours threshold was recognised as fairly arbitrary, but is drawn from what little evidence exists. It is impossible to define 'frequent coughing' given a subjective assessment which may take place weeks after the flight. Clinical judgement will have to be used in any such case to identify how many passengers to advise the airline to send information to.

Where the index case is a crew member, contact tracing of individual passengers is not necessary as passengers will have had minimal exposure.

12.4.5 RECOMMENDATIONS

R107 Following diagnosis of TB in an aircraft traveller, contact tracing of fellow passengers should not routinely be undertaken.

R108 The notifying clinician should inform the relevant consultant in communicable disease control (CCDC) if: D(GPP)

- less than three months has elapsed since the flight and the flight was longer than eight hours, *and*D(GPP)
- the index case is sputum smear positive, *and*D(GPP)
- the index case has MDR TB, *or*C
- the index case coughed frequently during the flight. D(GPP)

The CCDC should provide the airline with 'inform and advise' information to send to passengers seated in the same part[27] of the aircraft as the index case. D(GPP)

R109 If the TB index case is an aircraft crew member, contact tracing of passengers should not routinely take place. D(GPP)

2006

[27] Published evidence does not allow for a precise definition, but such contact tracing on aircraft has often only included people within three rows on either side of the index case.

R110 If the TB index case is an aircraft crew member, contact tracing of other members of staff is appropriate, in accordance with the usual principles for screening workplace colleagues (see section 12.4). B

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see chapter 11.
For details of contact tracing in general, see section 12.2.

12.5 Contact tracing: cases in schools

12.5.1 Clinical introduction

TB in school pupils or staff requires particular attention because of the potential for spread of infection and also because of the anxiety that may arise among pupils, parents, staff and others. They should all be subject to individual risk assessment following discussion with the consultant in communicable disease control.

If the index case of TB is an adult member of staff, the purpose is to detect secondary cases elsewhere in the school, while if it is a pupil, the purpose is not only to detect secondary cases but also to find the source case, if it is not already thought to be known.

12.5.2 Methodological introduction

Studies were included that attempted to establish whether contact tracing was effective in identifying latent and active tuberculosis in school contacts exposed to an index case of tuberculosis in the school setting.

Six cohort studies and four non-analytic studies were found. None of the cohort studies were conducted in the UK, and only one non-analytic study took place in the UK. One cohort study{11} and one non-analytic study{340} were excluded due to methodological limitations, which are presented in Appendix I. Despite limited reporting of participant baseline characteristics, five cohort studies{341–345} and three non-analytic studies{346–348} were included.

12.5.3 Evidence statements

Case yields of latent tuberculous infection

Six studies{341–343},{345},{347},{348} investigated case yields of latent TB infection in school pupils with differing levels of exposure to an index case of sputum smear-positive TB. Latent TB infection yield was reported for the following four exposure categories:

- schools with index cases of TB disease in comparison to control schools with no reported index cases
- school pupils exposed to index cases of TB disease in comparison to pupils with no exposure to index cases
- school pupils with different levels of classroom contact to index cases of TB disease
- school pupils with direct classroom contact to index cases of TB disease in comparison to pupils with no classroom exposure to index cases.

The evidence for latent TB infection is presented in Table 47.

Table 47: Detection of latent TB in schools contact tracing

Exposure category	Context of pupil exposure to TB index cases	Results N (%) pupils Mantoux test+	Association/statistical significance	Study location	Ref and NICE grade
1. Schools with pupil index cases*vs.*control schools	Four secondary schools *vs.* 10 secondary schools	277/3188 (8.7) *vs.* 123/3321 (3.7) [28][29]	$p<10^{-7}$	Italy	{343} 2+
	Two primary schools *vs.* three primary schools	51/722 (7.1) *vs.* 19/702 (2.7) [30]	NS	Canada	{344} 2+
2. Exposed*vs.*no	All current high	120/333 (36) *vs.*	RR 2.3 (95%CI 1.7 to 3.2, p<0.05)	USA	{342} 2+

[28] Tine Test positive
[29] BCG vaccination was discontinued in Italy before the present research cohort were born, so tine test positivity could not be attributed to the booster effect
[30] Prior BCG vaccination and foreign-born status were both significantly associated with Mantoux test positive outcome in all schools.

n- exposed school pupils (pupil index cases)	school pupils *vs.* non-exposed new school entrants	39/248 (16)			
	All high school graduates *vs.* non-exposed new school entrants	35/138 (25) *vs.* 39/248 (16)	RR 1.6 (95%CI 1.1 to 2.4, p<0.05)	USA	{342} 2+
	US-born current high school pupils *vs.* US-born new school entrants	27/145 (19) *vs.* 4/132 (3)	RR 6.1 (95%CI 2.2 to 17.9, p<0.05)	USA	{342} 2+
	US-born high school graduates *vs.* non-exposed US-born new school entrants	6/66 (9) *vs.* 4/132 (3)	RR 3.0 (95%CI 0.9 to 10.3)	USA	{342} 2+
3. Different levels of classroom exposure to pupil index cases	Junior high school pupils sharing one plus class *vs.* pupils entering a class recently vacated by index case	95/118 (81) *vs.* 30/88 (34)	Not reported	USA	{345} 2+
	Junior high school pupils sharing three *vs.* two *vs.*	9/9 (100) *vs.* 32/35 (91) *vs.* 55/74 (74)	Not reported	USA	{345} 2+

2006

	one class with index case				
	High school pupils sharing	7/13 (54) *vs.*	RR 5.7 (95%CI	USA	{341} 2+
	three plus *vs.* one plus (normally ventilated) *vs.* one plus (normal or enhanced ventilation) classrooms with index case	21/66 (32) *vs.* 25/106 (24)	3.26 to 10.13) *vs.* RR 4.2 (95%CI 2.6 to 6.75) *vs.* RR 3.2 (95%CI 2.0 to 5.18)		
4a. Pupils with*vs.*pupils without classroom exposure to pupil index cases	High school pupils sharing a classroom *vs.* pupils without classroom exposure	22/110 (20) *vs.* 54/616 (9)	RR 2.3 (95%CI 1.4 to 3.8)	USA	{342} 2+
	Secondary school pupils sharing a classroom *vs.* pupils without classroom exposure	76% tine test positive, nearly 11 times higher than pupils without classroom exposure	RR 10.9 (95%CI 8.7 to 13.4)	Italy	{343} 2+
	Primary school pupils sharing classrooms *vs.* pupils without classroom exposure	No significant difference in Mantoux test positive rates reported	Not reported	Canada	{344} 2+
4b. Pupils	Primary	12/28	Not reported	Ireland	{342},{343},{34

2006

with*vs.* pupils without classroom exposure to teacher index cases	school pupils sharing a classroom *vs.* pupils without classroom exposure	(43) *vs.* 3/27 (11)			7}, {348} 3+

Case yields of active tuberculous disease

Three studies{343},{344},{347},{348} investigated case yields of active TB disease in school pupils with differing levels of exposure to an index case of sputum smear-positive TB. Active disease in contacts was variably defined as

- abnormal chest X-ray{342},{343},{347},{348}
- not specified by test result or site of disease{344}
- presence/absence of positive AFB sputum smear or X-ray findings compatible with cavitary disease.{343}

Active TB disease case yield was reported for the following two exposure categories:

- schools with index cases of TB disease in comparison to control schools with no reported index cases
- school pupils exposed to index cases of TB disease in comparison to pupils with no exposure to index cases.

The evidence for active TB disease is presented in Table 48.

Table 48: Summary of evidence: detection of active TB in schools contact tracing

Exposure category	Context of pupil exposure to TB index cases	Results N (%) pupils with TB disease	Statistical significance	Study location	Ref and NICE grade
Schools with index cases*vs.* control schools	Four secondary schools *vs.* 10 secondary schools	14/3188 (0.4) *vs.* 1/3321 (0.03)	Not reported	Italy	{343} 2+
	Two primary schools *vs.*	1/722 (0.1) *vs*. 0/702	Not reported	Canada	{344} 2+

2006

	three primary schools				
Pupils with*vs.*pupils without classroom exposure to teacher index cases	Primary school pupils sharing a classroom *vs.* pupils without classroom exposure	8/28 (29) *vs.* 0/27	Not reported	Ireland	{342},{343},{347},{348} 3+

Case yields for a general TB outcome

One study conducted in the UK{342},{343},{347},{348} reported a general TB outcome (combined latent TB infection and active TB disease yield) for primary schools pupils with *vs.* those without classroom exposure to a teacher with sputum smear- and culture-positive tuberculous disease who developed symptoms over a three-month period prior to the outbreak.

31/46 (67%) pupils from two classrooms shared with the index case *vs.* 15/46 (33%) pupils from five non-exposed classrooms were diagnosed with TB infection or disease. No statistical significance testing was reported. (**3+**)

Transmission of tuberculosis disease from an index case to exposed school contacts verified by DNA fingerprint analysis

A study conducted in New Zealand{346} found that cases of active tuberculosis identified by contact tracing in secondary school pupils were confirmed by DNA fingerprint analysis to be due to direct transmission from school index cases. (**3+**)

12.5.4 From evidence to recommendations

There are the following potential difficulties in making recommendations from the evidence base.

- There is a possibility of publication bias in the evidence base, where reports of successful tracing are more likely to be of interest, and therefore the yield of these procedures is likely to be overestimated.

- The evidence base does not take into account the country of birth or ethnicity of pupils, which is likely to be a confounding factor. In schools with a large proportion of pupils drawn from populations with high rates of TB, latent

infection and active disease in some of those screened might erroneously be concluded as being due to transmission from the index case.

- Many of the studies conducted outside the UK were carried out in non-BCG vaccinated populations.

- Rates of disease are calculated on small denominators and are therefore imprecise.

The aim of contact tracing is different across age groups. In younger children a source is being sought, while in adolescents and adult staff members contact tracing is usually (but not invariably) the sole reason for the exercise.

The GDG were keen to limit the resources that might be consumed by these large and mainly unproductive exercises, and agreed that initially, only children in the same class as the index case need to be assessed. School registers may help in identifying the pupils at highest risk.

After-school, sports and religious activities should also be kept in mind where the degree of contact might be equivalent to classroom contact. The GDG agreed that outdoor activities would not normally pose a risk of TB transmission, unless this involved confined spaces for prolonged time periods, for example camping. Such obvious exceptions were not felt to require a recommendation.

12.5.5 RECOMMENDATIONS

R111 Following diagnosis of TB in a school pupil or member of staff, the CCDC should be prepared to explain the prevention and control procedures to staff, parents and the press. Advice on managing these incidents and their public relations is available from the HPU. D(GPP)

R112 If a school pupil is diagnosed with sputum smear-positive TB, the rest of his or her class (if there is a single class group), or the rest of the year group who share classes, should be assessed as part of contact tracing. B

R113 If a teacher has sputum-smear-positive TB, the pupils in his or her classes during the preceding three months should be assessed as part of contact tracing. C

R114 Clinicians conducting contact tracing in a school should consider extending it to include children and teachers involved in extracurricular activities, and non-teaching staff, on the basis of: D(GPP)

- the degree of infectivity of the index case
- the length of time the index case was in contact with others
- whether contacts are unusually susceptible to infection
- the proximity of contact.

R115 Secondary cases of sputum smear-positive TB should be treated as index cases for contact tracing (see R111–R114 above for class of recommendation).

R116 If the index case of a school pupil's TB infection is not found, and the child is not in a high-risk group for TB, contact tracing and screening (by either symptom enquiry or chest X-ray) should be considered for all relevant members of staff at the school. D(GPP)

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see section 11.6.
For details of contact tracing in general, see section 12.2.
If smear-positive TB is diagnosed in an adult working in community childcare, see section 12.6.
For examples of 'inform and advise' information, see Appendix H.

12.6 Contact tracing: community childcare

12.6.1 Clinical introduction

Children, particularly of pre-school age, are more likely to acquire TB infection, and progress to TB disease, than older children and adults if they are exposed to infectious tuberculosis –usually from adults. Each year in England and Wales there are a number of incidents where children in nurseries and other childcare facilities are screened for tuberculosis after exposure to an adult staff member. Government policy and social changes mean that more children will be found in childcare

settings. An increasing number of adults will therefore be in contact with children up to age 16 years.

12.6.2 Methodological introduction

Studies investigating whether there were specific management strategies that were effective in preventing and controlling the transmission of TB infection and disease in childcare settings were sought. One cohort study was found that addressed the question.

The study, conducted in a hospital nursery setting in the USA{349} focused on screening for tuberculosis in infants and healthcare workers exposed to an index case of TB disease. Selection of infants to different TB screening procedures was based on level of TB exposure. Mantoux test conversion rates in healthcare workers who worked in the nursery unit when the index case was present were compared with healthcare workers in the hospital who had not worked in the unit.

12.6.3 Evidence statements

Latent TB infection in infants and healthcare workers with high versus low risk of exposure to an index case of TB

No difference between high and low exposure groups in the number of tuberculin-positive reactions was identified.{349} The evidence is summarised in Table 49.

Table 49: Summary of evidence: detection of latent TB in community childcare

Patient group and exposure status	N (%) Mantoux test positive reactors in participants with low exposure to the index case	N (%) Mantoux test positive reactors in participants with high exposure to the index case	Statistical significance	NICE grade
Infants				
Low/high exposure shared unit with index case 8–12/0–8 weeks prior to diagnosis	1/259 (7 mm reaction at age 11 weeks, received BCG vaccination at age three days)	0/139 (including 30 aged more than 56 days)	Not reported	2+
Healthcare workers				
Low/high exposure never worked in unit/worked in unit during index case stay	14/619 (2.26) converted	4/130 (3.08) converted	NS p<0.6	2+

Completion rate for isoniazid prophylaxis among high-exposure infants
132/139 (95%) infants with high exposure to an index case of TB disease completed a three month course of isoniazid prophylaxis.{349} (**2+**)

12.6.4 From evidence to recommendations

There is no relevant evidence on which to base recommendations. Because of the lack of an infrastructure to provide screening for this very diverse setting, which includes informal care arrangements, recommendations deal only with contact tracing.

12.6.5 RECOMMENDATION

R117 When an adult who works in childcare (including people who provide childcare informally) is diagnosed with sputum smear-positive TB, management is as for contact tracing (see section 12.2). D(GPP)

12.7 Contact tracing: cases in hospital inpatients

12.7.1 Clinical introduction

With the increasing numbers of clinical cases of tuberculosis, some of whom are admitted to hospital, there are incidents where patients with tuberculosis are not appropriately isolated, leading to potential exposure of other patients, some of whom may have reduced immunity. Such incidents are not strictly outbreaks, but may consume considerable resources identifying exposed patients, many of whom are at minimal risk.

A further type of incident is where a healthcare worker is found to have active tuberculosis, with patients being exposed to possible infection risks. This latter type of incident often involves staff recruited from overseas, who may only have been screened to healthcare worker level and not to the higher level advised for new entrants from high-incidence settings (see section 12.1).

Finally, there have been true outbreaks where patients, usually but not exclusively HIV co-infected, have acquired active tuberculosis disease from other inpatients, often due to failure to use appropriate infection control measures, or because facilities thought to be negative pressure were not actually so.{232} Such outbreaks,

particularly when of MDR TB transmission, can have a high mortality and morbidity, as well as major medicolegal implications for NHS trusts.{232}

12.7.2 Methodological introduction

Studies that investigated whether contact tracing was effective in identifying latent tuberculosis infection and active tuberculosis disease in patient and staff contacts exposed to an index case of tuberculosis in the hospital setting were targeted.

One case control study and four non-analytic studies were identified. The case control study from the USA{350} evaluated a contact tracing investigation of hospital staff conducted in relation to an index patient diagnosed with tuberculosis disease from an extrapulmonary site. Despite limited reporting of baseline characteristics, and no significance testing for the outcome of Mantoux test converters in exposed cases and non-exposed controls, the study was included. Two non-analytic studies from the UK{351} and the USA{352} were included.

Three non-analytic studies from the USA{353} and the UK{232},{354} were excluded due to methodological limitations, which are presented in Appendix I.

12.7.3 Evidence statements

Case yields of latent tuberculous infection

Two studies{350},{352} investigated latent TB infection in staff with different levels of exposure to index cases of active TB disease in hospital settings. Neither of the studies was conducted in the UK.

The evidence for latent TB infection is presented in Table 50.

Table 50: Detection of latent TB in contact tracing among health care workers (HCWs)

Exposure category	Exposure content	Results Healthcare workers with Mantoux test conversions, N (%)	Association/statistical significance	Ref and NICE grade
Exposed*vs.*non-exposed healthcare workers (non-pulmonary patient index	Nurses exposed to index case after surgery *vs.* nurses and students	12/95 (13) *vs.* 2/1435 (0.14) *vs*. 0/23	Not reported	{350} 2+

2006

case)	exposed prior to surgery *vs.* non-exposed historical control nurses			
Exposed*vs.*non-exposed healthcare workers (healthcare workers index case)	Healthcare workers on two wards (A and B) *vs.* healthcare workers on non-exposed wards	Ward A 21/70 (30) *vs*. 10/76 (13.2) non-exposed wards	RR 2.3 (95%CI 1.2 to 4.5, p=0.02)	{352} 3+
		Ward B 29/61 (47.5) *vs.* 10/76 (13.2) non-exposed wards	RR 3.6 (95%CI 1.9 to 6.8, p<0.001)	{352} 3+
		Controlling for exposure to infectious TB patients (N=25): risk of Mantoux test conversion remained higher for healthcare workers on wards A and B	Weighted RR 3.0 (95%CI 1.9 to 4.5, p<0.001)	{352} 3+

Case yields of active tuberculous disease

Two studies{351},{352} investigated case yields of active TB disease in patients and staff in hospitals where index cases of active TB disease had been identified. One of the studies was conducted in the UK. Active TB disease case yields were reported for the following:

- staff with and without exposure to TB index cases
- hospital staff, surgical patients and renal patients exposed to a TB index case.

The evidence for active TB disease is presented in Table 51 below.

Table 51: Detection of active TB in contact tracing among healthcare workers

Population	Exposure to healthcare workers index cases	Results Healthcare workers with TB disease, N (%)	Statistical significance	Ref and NICE grade
Exposed*vs.*non-exposed healthcare workers	HCWs exposed on two wards (A and B) *vs.* Healthcare	8/51 (16) wards A and B *vs*. 0/76 non-exposed wards	Not reported	{352} 3+

	workers on non-exposed wards			
Healthcare workers*vs.*renal patients*vs.*surgical patients	All groups exposed in a hospital	0/135 *vs.* 1/220 (0.45%) *vs.* 0/57	Not reported	{351} 3+

Type of exposure to the index case

One study{350} found that exposure to the surgical wounds of an index case of non-pulmonary TB was significantly associated with latent TB among previously Mantoux test -negative nurses.

Irrigation or packing of the wound was the only statistically significant risk factor for a positive Mantoux test (OR 9, 95%CI 1.2 to 67, p=0.03), with nurses involved in these activities having nine times the risk of Mantoux test conversion compared to nurses not involved in substantial wound care. (**2+**)

Duration of exposure

Hospital staff Mantoux test converters and index cases worked more total shifts on two wards with infectious TB cases than staff who were Mantoux test negative (Ward A median 80 *vs*. four shifts, p=0.004; Ward B median 124 *vs.* five shifts, p<0.001).{352} (**3+**)

12.7.4 From evidence to recommendations

The wide variety of settings and possibilities mean that narrowly drawn guidelines are not appropriate. The pick-up from contact tracing exercises is very low so it is important to avoid unnecessary screening. Evidence from North America may show levels of potential transmission, but is not particularly relevant for the effectiveness of service models in the UK. The GDG's considerations were otherwise constrained by the paucity of evidence relevant to the UK.

Awareness of tuberculosis and transmission risks needs to be maintained in healthcare workers who work with immunocompromised patients – for example surgeons who work with transplant patients, and oncologists. A rigorous risk assessment was regarded as useful before any action is taken.

The GDG recognised the need to limit contact tracing exercises to instances where there is a genuine risk of TB transmission, and chose eight hours as a time

threshold for exposure. There is no evidence to support this, but it is in line with the threshold given elsewhere for contact tracing.

12.7.5 RECOMMENDATIONS

R118 Following diagnosis of TB in a hospital inpatient, a risk assessment should be undertaken. This should take in to account:

- the degree of infectivity of the index case
- the length of time before the infectious patient was isolated
- whether other patients are unusually susceptible to infection
- the proximity of contact.

Contact tracing and testing should be carried out only for patients for whom the risk is regarded as significant. D(GPP)

R119 Patients should be regarded as at risk of infection if they spent more than eight hours in the same bay as an inpatient with sputum smear-positive TB who had a cough. The risk should be documented in the contact's clinical notes, for the attention of the contact's consultant. The contact should be given 'inform and advise' information, and their general practitioner should be informed. D(GPP)

R120 If patients were exposed to a patient with sputum smear-positive TB for long enough to be equivalent to household contacts (as determined by the risk assessment), or an exposed patient is known to be particularly susceptible to infection, they should be managed as equivalent to household contacts (see section 12.2). D(GPP)

R121 If an inpatient with sputum smear-positive TB is found to have MDR TB, or if exposed patients are HIV positive, contact tracing should be in line with the Interdepartmental Working Group on Tuberculosis guidelines.{386}D(GPP)

R122 In cases of doubt when planning contact tracing after diagnosing sputum-smear-positive TB in an inpatient, further advice should be sought from the regional or national Health Protection Agency or people experienced in the field. D(GPP)

Cross-referring:
For details of diagnosing latent TB, see section 5.1.

For details of diagnosing active TB, see section 5.2.

For details of BCG vaccination, see section 11.6.

For details of contact tracing in general, see section 12.2.

For examples of 'inform and advise' information, see Appendix H.

12.8 New entrants screening (people recently arriving in or returning to the UK)

12.8.1 Clinical introduction

The five-yearly national notification surveys have consistently shown the highest rates of clinical tuberculosis disease in recent arrivals, particularly within the first few years after initial entry. This trend has been shown from 1978/9{355} through to 1998,{26} and in continuous enhanced surveillance from 1999–2002,{140} with 63% of all cases in 2001 being non-UK born. From 1978/9 to 1988 the great majority of people other than of white ethnicity with TB were of Indian subcontinent origin, but from 1988 onwards there has been a significant increase in the proportion of cases of black African origin, from 1.7% in 1988 to 13% in 1998, and most recently 21% in 2002.

Deficiencies in the official port of arrival system were recognised in these documents, with advice that local systems and information be used to augment new entrant identification. Screening for new entrants from settings of high incidence (defined as those with an incidence rate of at least 40/100,000) was advised. In practice this applied to all new entrants apart from those from the then European Union countries, Australia, New Zealand, Canada and the USA.{6}

Following identification of appropriate new entrants, the tools available for screening were the same as those for household contacts of cases of tuberculosis: enquiry about symptoms of (and any prior history of) tuberculosis, BCG history corroborated by documentation or scar, tuberculin skin testing and chest X-ray.{6} Interferon-gamma immunological tests were not available in the UK in the 1990s.

12.8.2 Current practice

The review of current services found that, where new entrants services were provided, it could be via a dedicated new entrants service, often a primary care-

based, holistic new entrants programme. Otherwise, new entrants may be seen in general TB clinics. Some clinics did not appear to have any provision for new entrant screening. The review did not cover the newer arrangements in fast-track induction centres for refugees, which are organised by the Home Office.

Outside London, 44% of service providers had a dedicated new entrant clinic and 35% saw new entrants in a general clinic, usually the BCG clinic. For two local services (3%), new entrants were seen at home. Other respondents had no specific new entrant screening programme. Within London, 55% had a dedicated clinic.

12.8.3 Methodological introduction

Studies that compared different service models of TB screening for new immigrants in order to evaluate which was most effective were targeted.

Two cohort studies from the UK{297},{356} and one cohort from the Netherlands{357} were found. None of the studies reported whether blinding of the investigators to the different service models being evaluated had taken place. Two studies, one from the UK{296} and one conducted in Italy,{358} were excluded due to additional methodological limitations listed in Appendix I.

In addition, there was a search for studies that compared different screening methods for latent and active tuberculosis in new immigrants and ethnic minority residents returning from settings with a high incidence of TB to evaluate which was most effective.

Three non-analytic studies were identified. One study{359} focused on symptom questionnaire and chest X-ray screening methods applied to a group of East Timor refugees screened on entry into Australia. A second study{360} examined the sensitivity of Mantoux test and chest X-ray for a subsequent diagnosis of active TB in Tibetan refugees entering the USA. A third study conducted in the USA{361} was excluded due to methodological limitations presented in Appendix I.

12.8.4 Evidence statements: service models

Proportions of new immigrants identified by different service models

Two studies{297},{356} compared the proportions of new immigrants screened for TB by different service models within the same area. Service models included:

- port of arrival identification
- primary care (GP or family practitioner) identification
- targeted screening of the homeless.

The evidence for the proportions of new entrants identified by the different models is presented in Table 52.

Table 52: Summary of evidence: models of new entrant screening

POA model, N (%) screened	Primary care model, N (%) screened	Homeless screening model, N (%) screened	Statistical significance	Ref and NICE grade
199 (48)	45 (11) – GPs	172 (41) – targeted screening	Not reported	{297},{356} 2+
905 (53)	787 (47) – family practitioner committee model	Not done	Not reported	{297},{356} 2+
4/103 (3.8) homeless new immigrants arriving in UK in previous two years	N/A	103/172 arrived in the UK in the previous two years	Not reported	{297},{356} 2+

Proportions of new immigrants identified with latent tuberculosis

In one study{356} the POA service model identified more new immigrants with weak tuberculin-positive reactions, but fewer with strongly positive Mantoux test reactions in comparison to targeted screening of homeless new immigrants and new immigrants screened in GP settings. The evidence is presented in Table 53.

Table 53: Detection of latent TB in contact tracing among new entrants

POA model, N (%) Heaf tested, Heaf grade	Primary care model, N (%) Heaf tested, Heaf grade	Homeless screening model, N (%) Heaf tested, Heaf grade	Statistical significance	NICE grade
100/181 (55) grade 2	14/39 (35) grade 2	84/172 (49) grade 2	Not reported	2+
9/181 (5) grade 3 or 4	8/39 (21) grade 3 or 4	13/172 (8) grade 3 or 4	Not reported	2+

Proportions of new immigrants identified with active tuberculosis

Two studies{356},{297} focused on comparing the proportions of new immigrants with active TB disease identified by different service models within the same area. Service models were:

- port of arrival identification
- primary care (GP or family practitioner) identification
- targeted screening of the homeless
- passive case finding.

The evidence is presented in Tables 54 and 55 below.

Table 54: Detection of latent TB in contact tracing among new entrants

Port of arrival model, N (%)	Primary care model, N (%)	Homeless screening model, N (%)	Statistical significance	Ref and NICE grade
3/181 (2)	0/39	0/172	Not reported	{297} 2+

Table 55: Detection of active TB disease in new entrants detected within the same five-year time period, N (%)

Port of arrival and primary care models combined	Primary case finding model	Statistical significance	Ref and NICE grade
11/57 (19)	27/57 (47.3)	Not reported	{356} 2+

Comparing hospital admissions and duration of symptoms in TB disease cases identified by new immigrant screening and passive case finding

One study{357} found that active TB cases detected by new immigrant screening had on average shorter duration of symptoms and fewer hospital admissions compared to TB patients detected by passive case finding. The evidence is presented Table 56.

Table 56: Symptoms and hospital admissions in new entrants identified with active TB

Outcome	New immigrant screening	Passive case finding	Association/statistical significance	NICE grade
Mean (median) duration of symptoms, all TB cases	4.2 (0) weeks	10.5 (7.5) weeks	p<0.001	2+
Mean (median) duration of symptoms, smear-positive cases only	4.2 (0) weeks	11.4 (6) weeks	p<0.001	2+
Mean (median) duration of symptoms,	4.6 (0) weeks	10.5 (8) weeks	p<0.001	2+

TB cases resident six plus months				
Hospital admissions, N (%)	91/446 (20) admitted	215/361 (60) admitted	OR 0.2 (95% CI 0.1 to 0.2)	2+

12.8.5 Evidence statements: screening methods

Effectiveness of symptom questionnaire in comparison to chest X-ray for predicting a diagnosis of active tuberculosis

One study from Australia{359} found that a symptom questionnaire was less accurate in predicting cases of active tuberculosis in East Timor refugees compared to chest X-ray.

Chest X-ray suggestive of TB was the only statistically significant predictor of a diagnosis of TB, with 95.8% of those diagnosed with TB having an abnormal chest X-ray (OR 2.76, 95%CI 1.25 to 6.07, p= 0.01). (**3+**)

Effectiveness of Mantoux tests in comparison to chest X-ray for predicting a diagnosis of active tuberculosis

One study from the USA{360} found that chest X-ray was significantly associated with cases of active TB in Tibetan refugees whereas the size of Mantoux test induration in the sample was not.

Chest X-ray abnormalities were associated with an increased risk of subsequent diagnosis of active TB (RR 6.78, p=0.005). (**3+**)

12.8.6 Health economic modelling

A decision analytic model was used to estimate the cost-effectiveness of alternative screening algorithms for new entrants from high-risk countries. The economic model was based on an initial algorithm which included initial screening for active disease using a symptom checklist with clinic follow-up for suspected cases, and skin testing for detecting latent infection in new entrants aged 35 or younger. It was assumed that prophylaxis would be offered to those with positive skin tests, and no active disease, and that BCG vaccination would be offered to people with a negative skin test and no evidence of prior BCG. The model included assumptions about the attendance and treatment concordance rates. We then estimated the cost-effectiveness of variations to the screening algorithm, and the overall cost-effectiveness of the algorithm as a function of the prevalence of active and latent TB

in the cohort, and the future incidence for people with/without latent infection at the time of screening.

The model used a simple decision tree approach, assuming a fixed number of secondary cases per primary case, rather than modelling the dynamics of transmission within the population. The results should thus be treated with caution. Caution is also required because of considerable uncertainty over various data inputs and assumptions, and also because of likely variation in programme effectiveness and costs in different areas. As far as possible, the model was based on best available empirical evidence. However, no data were available for some key parameters, so judgement from GDG members was used to estimate likely ranges of values.

It is important to recognise that the model does not take account of other potential benefits of screening – for example, community-based screening may act to introduce new entrants to local health services, and as a screen for other possible health problems. The model also does not take account of other ways in which screening and treatments could be better targeted. For example, the decision to offer prophylaxis could be informed by individuals' likely exposure to TB, risk factors for developing active TB, and/or evidence of latent infection from X-ray.

12.8.7 Cost-effectiveness of prophylaxis for suspected latent infection

The economic model suggests that prophylaxis is not cost-effective in the context of new entrant screening. Using the base case assumptions, the estimated incremental cost per QALY gained for including prophylaxis in the new entrant screening algorithm was nearly £400,000. This result was robust to variation in the model parameters.

Cost-effectiveness of BCG for Mantoux test -negative new entrants

The model predicts that BCG vaccination is cost-saving for the NHS in the context of new entrant screening. Removing vaccination for Mantoux test -negative new entrants from the new entrant screening algorithm would lead to a cost increase of £20,000 and a QALY loss of 1.8 per 100,000 screened, under the base case assumptions.

Symptom checklist vs. chest X-ray for detecting active disease

The cost-effectiveness of initial screening for active disease with a symptom checklist compared with chest X-ray depends on their relative costs and accuracies. Under the base case assumptions, the model suggests that although X-ray screening is more expensive, it leads to an overall saving in NHS expenditure due the lower number of false positive results that is predicted.

Interferon-gamma test vs. tuberculin skin test for latent infection

The model suggests that, despite its higher initial cost, interferon-gamma testing might be a cost-effective alternative to skin testing if it is demonstrated to give a lower number of false positive results. Under the base case assumptions, the model predicted that IGTs would be cost-saving in comparison with skin tests.

Cost-effectiveness of new entrant screening

At low levels of prevalent TB in the cohort tested, none of the screening algorithms was cost-effective. The algorithm without prophylaxis achieves an ICER of £30,000 per QALY at a TB prevalence of about 3%, and an ICER of £20,000 per QALY at about 4% prevalence. This is relatively high compared with rates of disease found in many new entrant screening programmes.

12.8.8 From evidence to recommendations

Current political policy aims for increasing use of chest X-ray screening for active TB prior to entry to the UK. This excludes children under 11 and women who might be pregnant. This NICE guideline addresses activities in the NHS, ie after arrival, and does not address services provided at the port of arrival or in induction centres for asylum seekers. However, the first consideration in screening is whether or not this pre-entry X-ray has been carried out and results are available. Readers are advised to check for new developments in these policies when interpreting the recommendations below.

The GDG were mindful of the legal restrictions on access to NHS services for overseas visitors, and the difficulty this introduces for screening. The data on comparisons of methods of screening is weak and does not show a clear best method. The GDG is aware of the rapidly developing field of interferon-gamma

testing for latent TB. Insufficient data is currently available on its utility in this setting to recommend its routine use at this stage.

National surveys up to 1998 and continuous enhanced surveillance since 1999 show the highest rates of TB in new arrivals. Some cases are found by X-ray screening at port of arrival, and some by new-entrant screening soon after arrival, but most cases arise at least one year after initial entry to the UK (see Appendix G for details).

The purpose of screening high-risk groups, such as arrivals from high-incidence settings (defined as an incidence of 40 cases/100,000 per annum), and all asylum seekers, is threefold.

1. To detect cases with active disease, particularly respiratory, to enable treatment to be given, and prevent secondary cases.

2. To detect those with tuberculosis infection, particularly children, for whom treatment for latent TB infection is appropriate.

3. To identify those with no evidence of tuberculosis infection who, if previously unvaccinated, may benefit from BCG vaccination.

The health economics in this area clearly indicate that targeting screening activities on the new entrants at highest risk of developing active TB is crucial if the screening is to be cost-effective to the NHS. However, the data are very limited and further economic research is needed to support policy in this area. The epidemiology shows that most cases of active TB in new entrants develop some time after arrival in the UK. There are also policy changes under way in terms of pre-entry screening for active TB. The GDG drafted the algorithm shown below to reflect their consensus on screening new entrants.

The process of identifying new entrants for screening through port of arrival notification to the local CCDC has limitations, and the recommendations therefore advise on different sources which can be used. This is relevant to conditions other than TB, but is not currently practised uniformly around the country, and therefore is specified here.

12.8.9 RECOMMENDATIONS

R123 Healthcare professionals, including primary care staff, responsible for screening new entrants[31] should maintain a coordinated programme to:

- detect active TB and start treatment B
- detect latent TB and start treatment B
- provide BCG vaccination to those in high-risk groups who are not infected and who are previously unvaccinated D(GPP)
- provide relevant information to all new entrants. D(GPP)

R124 New entrant screening for tuberculosis should be incorporated within larger health screening programmes for new entrants, linked to local services. D(GPP)

R125 Assessment for, and management of TB in new entrants should consist of the following. D(GPP). See also R5 for assessment of latent TB

- Risk assessment for HIV, including HIV prevalence rates in the country of origin, which is then taken into account for Mantoux testing and BCG vaccination.
- Assessment for active TB if interferon-gamma test is positive, which would include a chest X-ray.
- Treatment for latent TB infection for people aged 35 or younger in whom active TB has been excluded, with a positive Mantoux test inconsistent with their BCG history, and a positive interferon-gamma test.
- Consideration of BCG for unvaccinated people who are Mantoux negative (see section 11.4).
- 'Inform and advise' information for people who do not have active TB and are not being offered BCG or treatment for latent TB infection.

See the algorithm in Figure 12 for further detail.

2006

2006, amended 2011

[31] In this guideline, new entrants are defined as people who have recently arrived in or returned to the UK from high-incidence countries, as defined by the HPA; go to **www.hpa.org.uk** and search for 'WHO country data TB'.

R126 New entrants should be identified for TB screening from the following information:

- port of arrival reports D(GPP)
- new registrations with primary care B
- entry to education (including universities) D(GPP)
- links with statutory and voluntary groups working with new entrants. D(GPP)

R127 Any healthcare professional working with new entrants should encourage them to register with a GP. D(GPP)

Cross-referring:

For details of diagnosing latent TB, see section 5.1.

For details of diagnosing active TB, see section 5.2.

For details of BCG vaccination, see section 11.4

For examples of 'inform and advise' information, see Appendix H.

2006

This algorithm is currently being reviewed and has been temporarily removed.

2006, amended 2011

12.9 Street homeless people

12.9.1 Clinical introduction

Deprivation has long been associated with tuberculosis. Much higher rates of tuberculosis disease in street homeless people and hostel dwellers have been recognised for many years{362},{363}. Chest X-ray screening of homeless people attending a soup kitchen in London in 1993{364} showed 4.3% with X-ray changes suspicious of active tuberculosis of which 1.5% (1,500/100,000) were confirmed as having bacteriologically confirmed active disease. The great majority of such street homeless people in the UK up to the late 1990s were men of white ethnicity, whose rate of tuberculosis from national data would normally be expected to be in the range of 5/100,000 per annum.{26},{140}

12.9.2 Methodological introduction

Studies that compared different methods of screening for latent tuberculosis infection and active tuberculosis disease in homeless people in order to evaluate which method was most effective were targeted.

Six non-analytic studies focused on different tuberculosis screening methods applied to homeless participants. None of the studies reported the results of interferon-gamma immunological testing in homeless people. Four studies{308},{328},{365},{366} did not make comparisons between the different screening methods they reported and were excluded.

Two studies{367},{368} conducted in the UK and the USA compared homeless people diagnosed with active tuberculosis with their prior test results on symptom questionnaire, tuberculin skin test, and chest X-ray. The studies were included despite having the following methodological limitations.

- The number of people approached for screening and resultant screening uptake was not clearly reported.
- Not all tests were read and no explanation for this was provided.
- Some studies offered incentives to attend for screening, while others did not.
- Those involved in collecting prospective data via interviews were aware of retrospective findings that categorised subjects by clinical outcome.

- It was not reported how screening tests were conducted and read and by whom.
- Screening methods used did not show a combination of good sensitivity and specificity.
- Uptake of screening varied between 40–90% at different sites.
- Investigators did not state whether tests were performed blindly or independently.
- Statistical significance testing was not done.

12.9.3 Evidence statements

Comparative effectiveness of symptom questionnaire, tuberculin skin test and chest X-ray for detecting latent tuberculous infection

One retrospective study{367} found that tuberculin skin testing was more effective in detecting latent tuberculosis and eligibility for treatment for latent TB infection in homeless people than either symptom questionnaire or chest X-ray. The evidence is presented in Table 57.

Table 57: Summary of evidence: detection methods for latent TB

People with abnormal symptom questionnaire scores	People with positive tuberculin skin test results, Heaf grade 4	People with abnormal chest X-ray results	Statistical significance	NICE grade
0/5 with Heaf grade 4 (0% sensitivity)	5/5 prescribed treatment for latent TB infection (100% sensitivity)	0/5 with Heaf grade 4 (0% sensitivity)	Not reported	3+

Comparative effectiveness of symptom questionnaire, tuberculin skin test and chest X-ray for detecting active tuberculous disease

Two retrospective studies,{367},{368} did not find consistent evidence that any of the three screening methods compared were more effective than the others in detecting signs and symptoms of TB in homeless people subsequently diagnosed with active tuberculosis. Evidence is summarised in Table 58 below.

Table 58: Summary of evidence: detection methods for active TB

N (%) TB disease cases with abnormal symptom questionnaire scores	N (%) TB disease cases with tuberculin skin test positive scores	N (%) TB disease cases with abnormal chest X-ray results	Statistical significance	Ref and NICE grade
2/10 (20) reported	1/10 (10) (7/10	8/10 (80)	Not reported	{367},{368}

haemoptysis	cases did not have Mantoux test)			3+
13/16 (81), sensitivity 81%, specificity 51%, PPV 23%, NPV 94%	11/16 (69), sensitivity 69%, specificity 83%, PPV 42%, NPV 94%	5/16 (31), sensitivity 31%, specificity 94%, PPV 50%, NPV 88%	Not reported	{367};{368} 3+
PPV = Positive predictive value; NPV = Negative predictive value.				

12.9.4 From evidence to recommendations

The rate of TB in street homeless people is still high. This group is difficult to reach. Emphasis should therefore be on active case finding, which may have to be done on an opportunist and/or symptomatic basis. In urban settings, digital chest X-ray provides fast results for likely active disease.

Simple incentives for attending screening, such as hot drinks or snacks, may be useful. Because of the mobility of this group, tuberculin skin testing and interferon-gamma testing were felt to be less useful generally, because people may move before test reading and are also not likely to complete treatment for latent TB infection. The important role of the TB service was recognised in promoting awareness of TB, and who to contact, among those working with homeless people, including primary care professionals, and the social and voluntary sectors.

The GDG were unable to make a service configuration recommendation on the frequency of screening in this group, given the lack of any evidence to guide them.

12.9.5 RECOMMENDATIONS

R128 Active case finding should be carried out among street homeless people (including those using direct access hostels for the homeless) by chest X-ray screening on an opportunistic and/or symptomatic basis. Simple incentives for attending, such as hot drinks and snacks, should be considered. D(GPP)

R129 Healthcare professionals working with people with TB should reinforce and update education about TB, and referral pathways, to primary care colleagues, social workers and voluntary workers who work with homeless people. D(GPP)

Cross-referring:
For details of diagnosing active TB, see section 5.2.

13 Preventing infection in specific settings

13.1 Healthcare environments: new employees

13.1.1 Clinical introduction

Studies in the late 1980s suggested that the incidence of TB in healthcare workers, with the general exception of mortuary workers, was no higher than that of the general population.{369} More recently however a study found a twofold increased risk among healthcare workers.{300} Also more recently the NHS has been recruiting staff, particularly nurses, from developing countries with a high incidence of tuberculosis. This is acknowledged as an essential area for improvement in the 2004 Chief Medical Officer's TB Action Plan{2} which gives as a goal: 'achieve comprehensive occupational screening of healthcare workers joining the NHS'.

13.1.2 Methodological introduction

Studies on the prevention of TB transmission in newly employed staff in hospital settings were sought. Only one non-analytic study{370} met the inclusion criteria.

Studies focusing on pre-employment screening measures to prevent and control the transmission of TB in healthcare workers with HIV infection were also targeted. No evidence was found, and hence there are no evidence statements for this area.

13.1.3 Evidence statements

TB prevention and control measures in pre-employment occupational health screening

One retrospective non-analytic study{370} reported on the following interventions for pre-employment occupational health screening in West Midlands NHS hospitals:

- identification of new doctors eligible for TB screening
- identification of new doctors and nurses at risk for active tuberculous disease
- appropriateness of tuberculin skin testing for new employees.

Evidence is summarised in Table 59.

Table 59: Summary of evidence: pre-employment screening

Intervention	Occupational health service pre-employment screening	NICE grade

Doctors eligible for TB screening, N (%)	Identified 7/14 (50) new doctors who developed active TB disease during employment.	3+
Healthcare workers at risk for active TB disease, measured by Heaf test grade	• Did not act on evidence of TB transmission in newly appointed doctors, and found no evidence of TB transmission in newly- appointed nurses. • 3/7 new doctors Mantoux test positive (grades 3–4) subsequently diagnosed with active TB via self-referral with symptoms. • Six new nurses Mantoux test negative (grades range 0–2) subsequently diagnosed with active TB.	3+
Mantoux test, Heaf test	• Inappropriately applied Mantoux tests to 13/26 new employees. • Two without prior BCG vaccination were not tested and developed TB disease. • Nine with prior BCG vaccination were tested. • 1/2 with unknown BCG status was tested.	3+

13.1.4 From evidence to recommendations

This guideline is not intended to duplicate the guidance which was, at the time of writing, being drafted by the Department of Health ('Health clearance for serious communicable diseases: new health care workers').

The recommendations are also guided by the advice of the Chief Medical Officer to the NHS in England to 'achieve comprehensive occupational screening of healthcare workers joining the NHS'.{2}

There is a possibility that new employees in healthcare environments who have recently entered the UK can miss out on the advanced level of screening given to new entrants. In this regard, the recommendations refer the reader to the section of the guideline for new entrants.

Limitations in pre-employment screening techniques are reported in the evidence base. Consequently, the GDG agreed that symptoms should be screened first, possibly by questionnaire, as a way to identify any new staff who may have active tuberculosis. Chest X-rays are the first choice of test for those with signs or symptoms.

For the majority of new employees without any signs or symptoms, resources should be used effectively by carrying out an individual risk assessment and choosing screening techniques accordingly. This is familiar current practice for many occupational medicine departments.

The recommendations aim to make sure that new employees are screened before commencing work. It was noted that the NICE guideline cannot dictate screening techniques to non-NHS agencies, and also that such screening may be carried out in other countries with attendant difficulty in receiving documentation. However, the health risks associated with employing an infectious member of staff were deemed to warrant a thorough check before they start work.

The evidence base does not support a significant departure from the details of the recommendations in the BTS code of practice.{6}

Although the evidence is limited to hospitals, the recommendations are applicable to primary as well as secondary care, and to ancillary as well as clinical staff.

13.1.5 RECOMMENDATIONS

R130 Employees new to the NHS who will be working with patients or clinical specimens should not start work until they have completed a TB screen or health check, or documentary evidence is provided of such screening having taken place within the preceding 12 months. D(GPP)

R131 Employees new to the NHS who will not have contact with patients or clinical specimens should not start work if they have signs or symptoms of TB. D(GPP)

R132 Health checks for employees new to the NHS who will have contact with patients or clinical materials should include: D(GPP)

- assessment of personal or family history of TB

- symptom and signs enquiry, possibly by questionnaire
- documentary evidence of TB skin testing (or interferon-gamma testing) and/or BCG scar check by an occupational health professional, not relying on the applicant's personal assessment
- Mantoux result within the last five years, if available.

2006

R133 See R14–7 for screening new NHS employees for latent TB.

2006, amended 2011

R134 Employees who will be working with patients or clinical specimens and who are Mantoux negative (less than 6 mm) should have an individual risk assessment for HIV infection before BCG vaccination is given. D(GPP)

2006

R135 Employees new to the NHS should be offered BCG vaccination, whatever their age, if they will have contact with patients and/or clinical specimens, are Mantoux negative (less than 6 mm) and have not been previously vaccinated. D(GPP)

R136 Employees of any age who are new to the NHS and are from countries of high TB incidence, or who have had contact with patients in settings with a high TB prevalence should have an interferon-gamma test. If negative, offer BCG vaccination as with a negative Mantoux result (see R134 and R135). If positive the person should be referred for clinical assessment for diagnosis and possible treatment of latent infection or active disease. D(GPP)

2006, amended 2011

R137 If a new employee from the UK or other low-incidence setting, without prior BCG vaccination, has a positive Mantoux and a positive interferon-gamma test, they should have a medical assessment and a chest X-ray. They should be referred to a TB clinic for consideration of TB treatment if the chest X-ray is abnormal, or for consideration of treatment of latent TB infection if the chest X-ray is normal. D(GPP)

R138 If a prospective or current healthcare worker who is Mantoux negative (less than 6 mm), declines BCG vaccination, the risks should be explained and the oral explanation supplemented by written advice. If the person still declines BCG vaccination, he or she should not work where there is a risk of exposure to TB. The employer will need to consider each case individually, taking account of employment and health and safety obligations. D(GPP)

2006

R139 Clinical students, agency and locum staff and contract ancillary workers who have contact with patients or clinical materials should be screened for TB to the same standard as new employees in healthcare environments, according to the recommendations set out above. Documentary evidence of screening to this standard should be sought from locum agencies and contractors who carry out their own screening. D(GPP)

R140 NHS trusts arranging care for NHS patients in non-NHS settings should ensure that healthcare workers who have contact with patients or clinical materials in these settings have been screened for TB to the same standard as new employees in healthcare environments (see R130–R139). D(GPP)

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see section 11.5.
For examples of 'inform and advise' information, see Appendix H.

2006

This algorithm is currently being reviewed and has been temporarily removed.

2006, amended 2011

Figure 13 Algorithm for new NHS employees

13.2 Healthcare environments: occupational health

2006

13.2.1 Clinical introduction

TB is transmitted through the aerosol route. Hitherto, best practice in hospitals{6} has been that patients with suspected pulmonary tuberculosis are initially admitted to single rooms, vented to the outside, until their sputum status is known and risk assessments for infectiousness and MDR TB are made. The risk assessment should also take into account the immune status of other patients on the ward. These measures should greatly reduce the chance of transmission to staff, but surveys of infection control practice show poor adherence.{371}

Readers should be aware of the Health and Safety Executive guidance in this area, 'Biological agents: managing the risks in laboratories and healthcare premises' (available from **www.hse.gov.uk**).

13.2.2 Methodological introduction

Studies on the prevention of TB transmission in staff currently employed in hospital settings were sought. One cohort study and four non-analytic studies were found.

Five non-analytic studies from the USA{233},{372–375} were excluded due to methodological limitations, presented in Appendix IOne non-analytic study from the UK{371} while methodologically sound, was excluded as it addressed the extent to which TB infection control measures recommended by guidelines were applied in practice, but did not seek to evaluate the effectiveness of recommended measures.

One cohort study{376} and four non-analytic studies{235},{370},{377},{378} reported evidence on the following:

- effects of new infection control measures in reducing TB transmission in hospital workers
- the association between ventilation controls and tuberculin skin test conversion in hospital workers
- effectiveness of occupational health screening for identifying cases of active tuberculous disease in hospital workers
- effects of serial tuberculin skin tests in BCG vaccinated hospital workers.

Studies on screening measures to prevent and control the transmission of TB in employed healthcare workers with HIV infection were also targeted. No evidence was found that met the inclusion criteria, and hence there are no evidence statements for this area.

13.2.3 Evidence statements

Effects of new infection control measures in reducing tuberculosis transmission in hospital workers

Evidence statements are presented in Table 60.

Table 60: Summary of evidence: infection control measures

New infection control measures	Population	N (%) decrease in healthcare worker Mantoux test conversion	Association/statistical significance	Ref and NICE grade

		rate in response to new measures		
1) Introduction of new respiratory isolation rooms. 2) Ventilation with at least 25% fresh air in the work area. 3) Laminar airflow from staff to patients. 4) Plastic droplet shields for staff.	Emergency department staff (intervention group) *vs.* other hospital workers not benefiting from interventions	Baseline: 6/50 (12) *vs.* 51/2514 (2)	RR 5.9 (95% CI 2.7 to 13.1); absolute difference 10% (95% CI 1% to 19%).	{376} 2+
		Post-intervention: 0/64 *vs.* 36/3000 (1.2)	RR not calculable; absolute difference 1.2% (95% CI 1% to 2%)	{376} 2+
1) Higher diagnostic suspicion for infectious TB. 2) Stricter criteria for discontinuation of patient isolation. 3) Stricter criteria for patient adherence to isolation procedures and use of respiratory protection when outside isolation rooms. 4) Restriction of sputum induction and aerosolised pentamidine treatment to isolation rooms. 5) Expansion of anti-TB therapy to include at least two more drugs. 6) Improvements to negative pressure rooms. 7) Upgraded respiratory protection for employees. 8) Improvement in speed of return for diagnostic tests.	Susceptible healthcare workers on an HIV ward	Initial period 7/25 (28) to early follow-up 3/17 (18) to late follow-up period 0/23	p<0.01	{235} 3+

2006

The association between ventilation controls and tuberculin skin test conversion in hospital workers

Evidence statements are presented in Table 61.

Table 61: Summary of evidence: ventilation

Association	Mantoux test conversion rates in healthcare workers	Association/statistical significance	Ref and NICE grade
Ventilation in non-isolation rooms and risk of latent TB infection	Shorter time to conversion significantly associated with being in a non-isolation room with less than two air exchanges *vs.* a room with two plus air exchanges per hour.	Hazard ratio: 3.4 (95% CI 2.1 to 5.8)	{377} 3+
Ventilation in respiratory isolation rooms and risk of latent TB infection	No significant difference in time to conversion for isolation rooms with less than six air exchanges *vs.* those with six plus air exchanges per hour.	Hazard ratio: 1.02 (95% CI 0.8 to 1.3)	{377} 3+
Inadequate ventilation and risk of latent TB infection in nurses and housekeeping staff	Rates significantly associated with inadequately ventilated non-isolation and isolation rooms.	p<0.001	{377} 3+
Inadequate ventilation and risk of latent TB infection in respiratory therapists	Rates significantly associated with inadequate ventilated non-isolation and bronchoscopy rooms.	p<0.001	{377} 3+

Effectiveness of occupational health screening for identifying cases of active tuberculous disease in hospital workers

One study{370} found that occupational health screening in West Midlands NHS hospitals detected fewer cases of active TB in employees than self-referral or contact tracing exercises.

Over a three-year period occupational health surveillance detected one (3.8%) case of active TB *vs.* 23 (88%) TB cases who self-referred with symptoms, and two cases (7.6%) detected via contact tracing exercises. Statistical significance testing was not done. (**3+**)

Effects of serial tuberculin skin tests in BCG vaccinated hospital workers

One prospective study{378} found that an initial Mantoux test, followed by a repeat Mantoux test administered one week later to BCG vaccinated hospital employees

resulted in an increased diameter of induration for the repeat test relative to the first test when read at 48 hours. This was followed by a decreased induration for the repeat test relative to the first at 72 hours.

Mean induration diameter was 7.1 mm for test 1 *vs.* 14.9 mm for repeat test at 48 hours (mean change 7.8 mm; 95%CI 4.2 to 11.4 mm, p<0.001). There was no difference between the tests at 72 hours (mean induration diameter 9.5 mm at test 1 versus 9.7 mm on repeat test, mean change 0.2 mm; 95%CI −4.0 mm to 4.4 mm, p=0.93). (**3+**)

13.2.4 From evidence to recommendations

The evidence base is not easily applicable to a UK NHS setting. Studies to assess the impact of certain isolation and infection control procedures have been performed in North America, using tuberculin skin test conversion (not performed in this context in the UK) as a marker of infection. The population of staff on which these studies are performed is also generally not BCG vaccinated.

There is a duty on staff to report symptoms as part of protecting patients.{62},{379}

Annual reminders are appropriate as a regular intervention in selected staff members, and this is best done at the same time as other annual reminders, for example influenza vaccination. In staff in general, it was felt that the recommendations should promote awareness through 'inform and advise' information.

13.2.5 RECOMMENDATIONS

These recommendations set the standard for NHS organisations and therefore should apply in any setting in England and Wales where NHS patients are treated.

R141 Reminders of the symptoms of TB, and the need for prompt reporting of such symptoms, should be included with annual reminders about occupational health for staff who: D(GPP)

- are in regular contact with TB patients or clinical materials, *or*
- have worked in a high-risk clinical setting for four weeks or longer.

One-off reminders should be given after a TB incident on a ward.

R142 If no documentary evidence of prior screening is available, staff in contact with patients or clinical material who are transferring jobs within the NHS should be screened as for new employees (see section 13.1). D(GPP)

R143 The risk of TB for a new healthcare worker who knows he or she is HIV positive at the time of recruitment should be assessed as part of the occupational health checks. D(GPP)

R144 The employer, through the occupational health department, should be aware of the settings with increased risk of exposure to TB, and that these pose increased risks to HIV-positive healthcare workers. D(GPP)

R145 Healthcare workers who are found to be HIV positive during employment should have medical and occupational assessments of TB risk, and may need to modify their work to reduce exposure. D(GPP)

Cross-referring:
For details of diagnosing latent TB, see section 5.1.
For details of diagnosing active TB, see section 5.2.
For details of BCG vaccination, see section 11.5.
For examples of 'inform and advise' information, see Appendix H.

13.3 Prisons and remand centres

13.3.1 Clinical introduction

In some countries the prison system acts as an amplification system for tuberculosis, with infected inmates causing transmission both within the prison and also in the community after discharge – either while still infectious or without adequate treatment and follow-up arrangements (or both). TB in the prison system of England and Wales was not thought to be a significant problem in the 1980s.{380} Prisoners however are likely to disproportionately include those with social and deprivation risk factors for TB (for example, social exclusion or drug abuse).

More recently, TB in prisons has increased and one community prison in London has been shown to be involved with the transmission of TB in an ongoing isoniazid-resistant TB outbreak.{329}

The 2005 Chief Medical Officer's TB Action Plan{2} sets improvements in prison care as one of the essential activities to be undertaken in improving TB care: 'achieve good coverage of prisons, with arrangements in particular for rapid assessment of suspected cases, supervision of prisoners' TB treatment, and maintenance of uninterrupted care by liaising with the services in their new area of residence prior to their release'. It also calls for strengthened surveillance of TB in prisons.

Throughout this section, the guideline uses the following terminology: in the USA, *jails* mostly house pre-trial detainees or inmates with short-duration sentences, whereas *prisons* house sentenced inmates for longer durations. In the UK, pre-trial detainees are housed in *remand centres* until completion of the trial and sentencing, while sentenced inmates are located in *prisons*. Remand and sentenced prisoners are often mixed within local prisons. In all these circumstances, those detained are referred to as *prisoners*.

13.3.2 Current practice

The review of current services shows that TB service providers either care for prisoners in clinics, or go on prison visits. Prior to the integration of prison medical services into the NHS, prisons would typically have arrangements for secondary care with one local hospital trust. Excluding those that stated that there was no prison or remand centre in their area, about a third cared for prisoners in clinics and a slightly higher proportion undertook prison visits, although some of these were not routine.

13.3.3 Methodological introduction

Studies investigating whether there were effective strategies for the prevention and control of the transmission of TB infection and disease in prisons were targeted. Two randomised controlled trials{206},{208} and four non-analytic studies{381–384} were found. However, two of these{383},{384} were excluded due to methodological

limitations presented in Appendix I. The studies were all conducted in the USA in either prison or jail settings.

13.3.4 Evidence statements

Comparing strategies used in prisons to facilitate completion of prophylaxis in prisoners released back into the community

Two RCTs{206},{208} compared:

- one TB education session *vs.* one TB education session plus a financial incentive
- one TB education session *vs.* one TB education session plus a financial incentive *vs.* TB education sessions administered every two weeks for the duration of an inmate's stay.

The evidence is presented in Table 62.

Table 62: Summary of evidence: educational interventions in prisons

Outcomes	One TB education session control	TB education session plus financial incentive	TB education sessions administered every 2 weeks	Association/statistical significance	Ref and NICE grade
N (%) attendance at follow-up community clinic appointment	7/30 (23.3)	8/31 (25.8)	N/A	NS OR 1.43 (95% CI 0.35 to 3.71, p=0.82)	{206} 1+
	25/104 (24)	42/114 (37)	40/107 (37)	Adjusted OR (pooled results for education and incentive groups): 1.85 (95% CI 1.04 to 3.28, p=0.04)	{208} 1+
N (%) completed prophylaxis	2/31	2/30	N/A	Not reported	{206} 1+
	12/25 (48)	14/42 (33)	24/37 (65)	p=0.02	{208}1 +
			Over twice as likely to complete than control group	Adjusted OR 2.2 (95% CI 1.04 to 4.72, p=0.04)	{208} 1+
		Completion no different from control		Adjusted OR 1.07 (95% CI 0.47 to 2.4)	{208} 1+

		group			

Strategies used to facilitate prevention and control of TB infection and disease within prisons

One non-analytic study{381} investigated the use of screening strategies to detect TB disease in incarcerated inmates.

The evidence is summarised in Table 63.

Table 63: Summary of evidence: detection of active TB in prisons

Population	Prior history/TB symptom reports	Routine TB screening (Mantoux test and chest X-ray)	Cases detected by contact tracing	Statistical significance	NICE grade
N (%) new inmates	13/53 (24)	39/53 (74)	N/A	Not reported	3+
N (%) longer-term inmates (≥ six months)	31/43 (72)	8/43 (19)	4/43 (9)	Not reported	3+

Over the five-year study period, entry screening of 87,518 new prisoners identified 53/55 (96% sensitivity) TB disease cases in this group. (**3+**)

Another non-analytic study{382} reported on the following screening procedures to detect TB disease in new prisoners:

- routine tuberculin skin tests
- routine chest X-ray tests
- use of isolation for prisoners with suspected TB disease.

The evidence is presented in Table 64.

Table 64: Summary of evidence: process of detecting active TB in prisons

	Mantoux test screening period	Chest X-ray screening period	Statistical significance	NICE grade
Detection of cases treated for TB disease, N	8 (denominator not reported)	8/1,830	Not reported	3+
Average time to isolation of suspected TB cases, hours	Exceeded 96 hours	24 hours or less[32]	Not reported	3+

[32] Change in protocol from use of Mantoux test to use of chest X-ray screening eliminated the waiting period for reading Mantoux test results.

Prisoners placed in isolation, N (%)	8/72 (11)	64/72 (89%)[33]	Not reported	3+

13.3.5 From evidence to recommendations

Other than limited data on measures to enhance treatment for latent TB infection in prisoners in the USA, there was little good-quality data in this area. There was a small amount of data to suggest that questionnaires are better than X-rays on initial screening, but that chest X-rays were better for screening symptomatic patients during imprisonment.

It is important to raise awareness of signs and symptoms in prisoners, prison staff and healthcare workers working in prisons and remand centres.

A lack of continuity of care over transfer between prisons and release to the community was seen as a major barrier to treatment completion, and prison medical services should take responsibility for having arrangements in place before either transfer or release.

There is a risk of drug resistance and the possibility of non-adherence, and accordingly DOT is recommended for all prisoners and detainees.

In addition, there is a risk to prison staff, and a level of occupational health equivalent to that of healthcare workers is recommended.

The current practice of taking three sputum samples within 24 hours for microscopy, including a morning sputum sample is supported in the recommendations.

The GDG considered the possibility of screening and BCG vaccination in young offenders' institutions, but agreed that the low number of cases that would be detected could not justify this.

13.3.6 RECOMMENDATIONS

R146 Healthcare workers providing care for prisoners and remand centre detainees should be aware of the signs and symptoms of active TB (see section 5.2). TB services should ensure that awareness of these signs and symptoms is also promoted among prisoners and prison staff. D(GPP)

2006

[33] Only 7/16 inmates ultimately met the case definition for active TB disease for both periods.

R147 Prisoners should be screened for TB by:

- a health questionnaire on each entry to the prison system, *then*D(GPP)
- for those with signs and symptoms of active TB, a chest X-ray, C and three sputum samples taken in 24 hours for TB microscopy, including a morning sputum sample (see section 5.2). D(GPP)

R148 All prisoners receiving treatment for active or latent TB should receive DOT. D(GPP)

R149 Prison medical services should have liaison and handover arrangements to ensure continuity of care before any prisoner on TB treatment is transferred between prisons. D(GPP)

R150 If a prisoner is being treated for active or latent TB, the prison medical services should draw up as early as possible a contingency plan for early discharge, which could happen directly from a court appearance. This plan should include firm arrangements for clinical follow-up and treatment monitoring in the intended district of residence, and should take into account that there may not be a fixed residence arranged for the prisoner after release. The prisoner should be given contact details for a named key worker, who will visit and monitor the prisoner after release and liaise between services involved. D(GPP)

R151 Prison service staff and others who have regular contact with prisoners (for example, probation officers and education and social workers) should have pre- and on-employment screening at the same level as for healthcare workers with patient contact (see sections 13.1 and 13.2). D(GPP)

14 Notification and enhanced surveillance

This chapter sets out the facts of national systems of data collection for TB, as co-ordinated and reported by the HPA's Centre for Infections. Recommendations are not made in this section; readers are reminded that notification is a statutory requirement.

14.1 Tuberculosis surveillance

TB surveillance aims to provide information that can be acted on to prevent and control tuberculosis. High-quality surveillance, as defined in the national TB Action Plan aims to provide the information required at local, national and international levels to:

- identify outbreaks (and other related incidents) and guide immediate action
- monitor trends and measure the occurrence of disease and anti-TB drug resistance
- inform policy
- inform development of services, and
- monitor the success of the TB programme.

Surveillance should also aim to identify population characteristics that predispose to a higher risk of infection and disease in order to appropriately target public health action and health services.

Monitoring the prevalence of infections should be part of surveillance of TB. However, in countries with low disease incidence, high immigration and generalised use of BCG, prevalence surveys on TB infection are very difficult to perform and interpret. Therefore tuberculosis surveillance is mainly based on morbidity associated with disease. It does however also include mortality information (derived from cause of death certification) as annual notifications of infectious diseases (NOIDs) deaths in residents of England and Wales (Office for National Statistics).

Information for TB case reports is currently mainly based on statutory notifications (NOIDs) implemented in 1913 and Enhanced Tuberculosis Surveillance (ETS) implemented in 1999. Treatment outcome monitoring was implemented as part of ETS in 2002. Information on tuberculosis isolates is based on MycobNet (Mycobacterial Surveillance Network) developed in 1994, which collates information on all isolates of *M. tuberculosis* complex confirmed at reference centres for mycobacteriology, including species and drug susceptibility results. On a yearly basis, data on TB cases reports from ETS are linked at national level with information from MycobNet on initial isolates in order to improve the completeness

of laboratory information (including drug susceptibility results) among TB incident cases.

The case definition used to identify incident cases to be included in the reporting system (NOIDs and ETS) is shown overleaf.

Tuberculosis surveillance is constantly evolving to reflect information needs at local and national levels, and availability of new microbiological and information technology. Some new systems are currently under development, including a national microbiological strain typing database and a national TB incidents and outbreaks database (TBIOS), both of which are held at the HPA's Centre for Infections.

All new tuberculosis cases (culture-confirmed cases and other than culture confirmed cases) should be reported.
A **culture-confirmed case** is defined as culture confirmed disease due to *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis* or *M. africanum*).
A **case other than culture confirmed** is defined as a case, that in absence of culture confirmation, meets the following criteria:

1. clinician's judgement that the patient's clinical and/or radiological signs and/or symptoms are compatible with tuberculosis,
2. *and*
3. clinician's decision to treat the patient with a full course of anti-tuberculosis treatment.

Persons receiving preventive chemoprophylaxis are not to be reported to NOIDs or ETS (but may be reported by letter if this information is required locally for service audit or other purposes).

14.2 Statutory notifications of infectious diseases

It is a statutory requirement in England, Wales and Northern Ireland for the diagnosing clinician to notify all cases of clinically diagnosed tuberculosis, whether or not microbiologically confirmed. This statutory requirement for the notification of certain infectious diseases came into being in 1891 and included TB from 1913. Notification must be made to the local 'proper officer', usually the CCDC. Regular returns are made by the proper officer to the Centre for Infections where NOIDs data are collated.

The prime purpose of the NOIDs system is speed in detecting possible outbreaks and epidemics, rather than accuracy of diagnosis. Since 1968 clinical suspicion of a notifiable infection is all that is required, but if a clinical diagnosis of TB later proves incorrect it should be denotified to the local proper officer. The data from this system is the most timely information about TB cases available but is not the most comprehensive or reliable. The dataset is very limited and errors are introduced through problems with removing duplicate entries and excluding, through denotification, cases wrongly diagnosed as TB.

14.3 Enhanced Tuberculosis Surveillance in England, Wales and Northern Ireland

ETS commenced on 1 January 1999 in England and Wales, and the following year in Northern Ireland. Its aims are to continuously provide detailed and comparable information on the epidemiology of tuberculosis, and to enable more precise estimates to be made of trends in tuberculosis incidence in subgroups of the population. ETS is less timely than NOIDs but in this system checking and de-duplication of cases is possible, providing a more accurate number of cases reported as well as more detailed information on each case. The minimum dataset on each case currently includes notification details and demographic, clinical and microbiological information. Cases are reported by clinicians to local coordinators in HPU, then via HPA regional units to the HPA Centre for Infections, Colindale. In most of the regions/countries ETS data are collected through a paper form, entered at local level or at regional level, to then be imported into a national database. The exact process varies according to the HPU or region. For example, in London these data are collected through a internet-based register. ETS provides an annual corrected analysis of reports by age, sex, ethnic group, country of birth, site of disease and region.

14.4 Treatment outcome monitoring in England, Wales and Northern Ireland

Outcome surveillance is an essential tool to determine the effectiveness of the national effort to control TB by providing a valuable insight into the proportion of patients who either complete treatment, die, experience complications resulting in

changed or prolonged drug therapy, or who are lost to follow-up prior to finishing treatment.

Tuberculosis treatment outcome surveillance is the last component of the ETS system and began, following pilot work, in January 2002 on TB cases reported in 2001. Information on outcome of treatment is collected on all TB cases reported at twelve months after starting treatment, or after notification where the treatment starting date is not available.

14.5 MycobNet (UK)

The UK's Mycobacterial Surveillance Network (MycobNet) was developed in 1994 in response to the need for effective information on the antibiotic susceptibility profile of TB cases. A specimen taken from the patient is tested at the local hospital laboratory and if found, or suspected, to be mycobacteria is forwarded to one of seven regional reference centres for mycobacteriology for further investigation.

Information gathered on isolates identified as *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis* or *M. africanum*) is collated through MycobNet at the HPA Centre for Infections, and includes species, drug sensitivity results, and some demographic and clinical data. This information is used to monitor trends in drug resistance in TB, and is also the basis of surveillance of *M. bovis* disease in humans.

15 Priorities for future research

Research recommendation 1

A diagnostic and qualitative study, assessing whether interferon-gamma tests are acceptable to patients and more effective than tuberculin skin tests for:

- predicting subsequent development of active TB, *or*
- diagnosing or ruling out current active TB

- new entrants from high TB prevalence countries
- healthcare workers
- children in high-risk areas who missed neonatal BCG
- contacts of sputum smear-positive TB

• HIV-positive patients.	
Population	• New immigrants from high TB prevalence countries. • Healthcare workers. • Children in high-risk areas who missed neonatal BCG. • Contacts of sputum-positive TB. • HIV-positive patients.
Intervention	Interferon-gamma tests.
Comparison	Tuberculin skin tests.
Outcome	Subsequent development of active TB. Qualitative patient acceptability outcome.

Research recommendation 2

A cluster RCT of DOT compared with self-administered treatment for latent and/or active TB should be conducted in a UK population. This should be targeted at homeless people, and those with a history of non-adherence, alcoholism, drug abuse or mental illness.	
Population	Homeless people, those with a history of non-adherence, alcoholism, drug abuse, or mental illness.
Intervention	DOT.
Comparison	Self-administered treatment.
Outcome	Treatment completion, cure and relapse rates.

Research recommendation 3

A study is needed of people found by new entrant screening (as set out above in 12.7) to be Mantoux positive and interferon-gamma positive, to establish better estimates of the cost-effectiveness of screening and treatment for latent TB infection in this population. This could identify factors predisposing people to developing active TB so that more effective targeted treatment programmes can be developed for latent TB infection..	
Population	New entrants with latent TB infection.
Intervention	Screening and treatment for latent TB infection.
Comparison	Not applicable.
Outcome	Risk factors for the development of active TB and the cost-effectiveness of screening and treatment for latent TB infection (£/QALY).

Research recommendation 4

A case control study, comparing people who developed active or latent TB with those who did not, and comparing the proportions of people in each group who had been vaccinated and the time since vaccination. The aim will be to derive improved estimates of protective efficacy and duration of protection of the BCG vaccine.	
Population	Patients eligible to receive BCG vaccine (this could be neonates, contacts, healthcare workers, new immigrants, schoolchildren).
Intervention	BCG.
Comparison	No BCG.
Outcome	Development of active TB. Possibly the development of latent TB infection as assessed by interferon gamma test (to avoid BCG effects

	on Mantoux test).

Research recommendation 5

A study to ascertain quality-of-life score estimates from those with TB (both active disease and latent infection) including adverse treatment effects, using an appropriate, quality-of-life instrument. This will improve economic decision-making throughout TBcare.	
Population	Those with TB disease or latent infection.
Intervention	Quality of life instrument.
Comparison	None.
Outcome	Quality of life score (single score estimate of health status).

Research recommendation 6

Research is needed to determine whether contact tracing is more effective (in terms of identifying cases of latent infection and active disease) among household contacts than among street homeless contacts of patients with confirmed TB disease (including those using direct-access hostels for the homeless).	
Population	• pulmonary smear-positive TB • pulmonary smear-negative TB • non-pulmonary TB.
Intervention	Contact screening of household contacts.
Comparison	Contact screening of homeless contacts.
Outcome	Case yields for latent TB infection and active TB disease among screened contacts.

Research recommendation 7

Research is needed to determine whether Port of Arrival scheme referrals with incentives for attending screening identify more cases of latent TB infection and active TB disease in new entrants than Port of Arrival scheme referrals with no incentives.	
Population	New immigrants from high TB prevalence (40+/100,000) countries.
Intervention	Port of arrival referrals with screening attendance incentives.
Comparison	Port of arrival referrals with no screening attendance incentives.
Outcome	Case yields for TB infection and active TB disease in intervention and comparison groups.

Research recommendation 8

Research is needed to determine whether incentives for attending chest X-ray screening achieve better coverage in the homeless population, or identify more cases of latent TB infection and active TB disease, than no incentives.	
Population	Individuals in temporary accommodation, hostels, and street homeless.
Intervention	Invitation with incentives to attend chest X-ray screening.
Comparison	Invitation without incentives to attend chest X-ray screening.
Outcome	Case yields for TB infection and active TB disease in intervention and comparison groups.

Other potential research recommendations

These are other topics where evidence is lacking, and where new research could improve future guidelines. They are not developed to the extent of the eight priorities above.

- A multicentre RCT in patients with bacteriologically confirmed tuberculous meningitis, comparing six to 11 months of chemotherapy with 12 months of treatment to ascertain if different treatment duration affects mortality and residual disability.

- Effectiveness of skills training for TB key workers, eg in motivational interviewing methods.

- An RCT of prisoners being treated for TB disease or latent infection who are discharged early, to assess whether contingency plans are cost-effective and improve treatment completion, cure and relapse rates.

- Is contact tracing using one method (eg home screening and follow-up of contacts) more effective than another (eg clinic-based screening and follow-up of contacts) in identifying cases of latent infection and active TB disease among adult and child household contacts of patients with confirmed TB disease?

- What is the impact of screening casual (low exposure) *vs.* close (high exposure) contacts of patients with confirmed TB on the yield of latent tuberculosis infection and active TB disease cases?

- Does screening of patient contacts in the same hospital bay as a pulmonary smear-positive index case of TB yield more cases of latent TB infection and active disease compared to other patient contacts on the same hospital ward?

A number of studies were suggested in areas not addressed by guideline questions, therefore the current evidence base for these areas is not known. These were:

- a study investigating risk factors for adverse outcomes from tuberculosis (deaths, acquired resistance and loss to follow-up)

- studies on patient and healthcare delay, to identify how to shorten the period of infectivity of active cases
- a diagnostic study of the efficacy of interferon-gamma testing in confirming active non-respiratory tuberculosis if other tests have remained inconclusive
- a study on whether interferon-gamma tests are more effective than chest X-ray screening for identifying cases of active TB disease in new immigrants undergoing TB screening.

16 References 2006

1. National Institute for Health and Clinical Excellence. *Guideline development methods: information for national collaborating centres and guideline developers.* London: NICE, 2005. Available from www.nice.org
2. Department of Health. *Stopping tuberculosis in England: an action plan from the Chief Medical Officer.* London: DH, 2004
3. Department of Health, The Scottish Office, The Welsh Office. *Immunisation against infectious diseases 1996 – the Green Book.* London: HMSO, 1996.
4. National Collaborating Centre for Chronic Conditions. *Tuberculosis: guideline development methodology pack.* London: NCC-CC, 2004.
5. British Medical Association, Royal Pharmaceutical Society of GB.*British National Formulary; no. 48.* London: Pharmaceutical Press, 2004
6. Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. *Thorax* 2000;55(11):887–901.
7. Ormerod LP, Joint Tuberculosis Committee of the British Thoracic Society. Serial surveys of the tuberculosis nursing and support provision in the high incidence districts of England and Wales. *Communicable Disease & Public Health* 2002;5(4):336–337.
8. Pozniak AL, Miller RF, Lipman MC. *BHIVA treatment guidelines for TB/HIV infection.* London: British HIV Association, 2005.
9. Brock I, Weldingh K, Lillebaek T, Follman F, Anderson P. Comparison of a new specific blood test and the skin test in tuberculosis contacts. *American Journal of Respiratory & Critical Care Medicine* 2004; 170(1):65–69.
10. Chapman AL, Munkanta M, Wilkinson KA, Pathan AA *et al.* Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of *Mycobacterium tuberculosis*-specific T cells. *AIDS* 2002;16(17):2285–2293.
11. Ewer K, Deeks J, Alvarez L, Bryant G *et al.* Comparison of T-cell-based assay with tuberculin skin test for diagnosis of *Mycobacterium tuberculosis* infection in a school tuberculosis outbreak. *Lancet* 2003; 361(9364):1168–1173.
12. Ferrara G, Losi M, Meacci M, Meccugni B *et al.* Routine hospital use of a commercial whole blood interferon-gamma assay for tuberculosis infection. *American Journal of Respiratory & Critical Care Medicine* 2005;172:631–635.
13. Hill PC, Brookes RH, Fox A, Fielding K *et al.* Large-scale evaluation of enzyme-linked immunospot assay and skin test for diagnosis of *Mycobacterium tuberculosis* infection against a gradient of exposure in the Gambia. *Clinical Infectious Diseases* 2004;38(7):966–973.
14. Johnson PD, Stuart RL, Grayson ML, Olden D *et al.* Tuberculin-purified protein derivative-, MPT-64-, and ESAT-6-stimulated gamma interferon responses in medical students before and after *Mycobacterium bovis* BCG vaccination and in patients with tuberculosis. *Clinical & Diagnostic Laboratory Immunology* 1999;6(6):934–937.
15. Kang YA, Lee HW, Yoon HI, Cho B *et al.* Discrepancy between the tuberculin skin test and the whole-blood interferon gamma assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. *Journal of the American Medical Association* 2005;293(22):2756–2761.
16. Lalvani A, Pathan AA, McShane H, Wilkinson RJ *et al.* Rapid detection of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells. *American Journal of Respiratory & Critical Care Medicine* 2001;163(4):824–828.
17. Lalvani A. Enhanced contact tracing and spatial tracking of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells. *Lancet* 2001;357(9273):2017–2021.
18. Pai M, Gokhale K, Joshi R, Dogra S *et al. Mycobacterium tuberculosis* infection in health care workers in rural India: comparison of a whole-blood interferon gamma assay with tuberculin skin testing. *Journal of the American Medical Association* 2005;293(22):2746–2755.

19. Richeldi L, Ewer K, Losi M, Bergamini BM *et al.* T cell-based tracking of multidrug resistant tuberculosis infection after brief exposure. *American Journal of Respiratory & Critical Care Medicine* 2004;170(3): 288–295.

20. Pai M, Riley LW, Colford JM, Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: *a* systematic review. *Lancet Infectious Diseases* 2004;4(12):761–776.

21. Department of Health. *Immunisation against infectious disease – the 'Green Book'.* London: DOH, 2006.

22. Davies PD. *Clinical Tuberculosis. Third ed.* London: Arnold, 2003.

23. El Sony A, Enarson D, Khamis A, Baraka O, Bjune G. Relation of grading of sputum smears with clinical features of tuberculosis patients in routine practice in Sudan. *International Journal of Tuberculosis & Lung Disease* 2002;6(2):91–97.

24. Brandli O. The clinical presentation of tuberculosis. *Respiration* 1998;65(2):97–105.

25. Wisnivesky JP, Kaplan J, Henschke C, McGinn TG, Crystal RG. Evaluation of clinical parameters to predict *Mycobacterium tuberculosis* in inpatients. *Archives of Internal Medicine* 2000;160(16):2471–2476.

26. Rose AM, Watson JM, Graham C, Nunn AJ *et al.* Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998. *Thorax* 2001;56(3):173–179.

27. Kumar D, Watson JM, Charlett A, Nicholas S, Darbyshire JH. Tuberculosis in England and Wales in 1993: results of a national survey. *Thorax* 1997;52:1060–1067.

28. Davies PD, Humphries MJ, Byfield SP, Nunn AJ *et al.* Bone and joint tuberculosis: a survey of notifications in England and Wales. *Journal of Bone & Joint Surgery (BR)* 1984;66(3):326–330.

29. Hodgson SP, Ormerod LP. Ten-year experience of bone and joint tuberculosis in Blackburn 1978-1987. *Journal of the Royal College of Surgeons of Edinburgh* 1990;35(4):259–262.

30. Mukherjee P, Singhal AK. Intestinal tuberculosis: 500 operated cases. *Proceedings of the Association of Surgeons of East Africa* 1979;2:70–75.

31. Khan MR, Khan IR, Pal KM. Diagnostic issues in abdominal tuberculosis. *Journal of the Pakistan Medical Association* 2001;51(4):138–142.

32. Klimach OE, Ormerod LP. Gastrointestinal tuberculosis: *a* retrospective review of 109 cases in a district general hospital. *Quarterly Journal of Medicine* 1985;56(221):569–578.

33. Sherman S, Rohwedder JJ, Ravikrishnan KP, Weg JG. Tuberculous enteritis and peritonitis: report of 36 general hospital cases. *Archives of Internal Medicine* 1980;140(4):506–508.

34. Bastani B, Shariatzadeh MR, Dehdashti F. Tuberculous peritonitis: report of 30 cases and review of the literature. *Quarterly Journal of Medicine* 1985;56(221):549–557.

35. Anand AC, Patnaik PK, Bhalla VP, Chaudhary R *et al.* Massive lower intestinal bleeding: a decade of experience. *Tropical Gastroenterology* 2001;22(3):131–134.

36. The Medical Research Council Tuberculosis and Chest Diseases Unit. National survey of tuberculosis notifications in England and Wales in 1983: characteristics of disease. *Tubercle* 1987;68(1):19–32.

37. Sutherland AM. Gynaecological tuberculosis: analysis of a personal series of 710 cases. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1985;25(3):203–207.

38. Yates VM, Ormerod LP. Cutaneous tuberculosis in Blackburn district (U.K.): a 15-year prospective series, 1981–95. *British Journal of Dermatology* 1997;136(4):483–489.

39. Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. *International Journal of Tuberculosis & Lung Disease* 2002;6(12): 1038–1045.

40. Joint Tuberculosis Committee of the British Thoracic Society. Management of opportunistic mycobacterial infections: joint tuberculosis committee guidelines 1999. *Thorax* 2000;55:210–218.

41. Klein NC, Duncanson FP, Lenox TH, III, Pitta A *et al.* Use of mycobacterial smears in the diagnosis of pulmonary tuberculosis in AIDS/ARC patients. *Chest* 1989;95(6):1190–1192.

42. Merrick ST, Sepkowitz KA, Walsh J, Damson L *et al.* Comparison of induced versus expectorated sputum for diagnosis of pulmonary tuberculosis by acid-fast smear. *American Journal of Infection Control* 1997; 25(6):463–466.

43. Yajko DM, Nassos PS, Sanders CA, Madej JJ, Hadley WK. High predictive value of the acid-fast smear for *Mycobacterium tuberculosis* despite the high prevalence of *Mycobacterium avium* complex in respiratory specimens. *Clinical Infectious Diseases* 1994;19(2):334–336.

44. Finch D, Beaty CD. The utility of a single sputum specimen in the diagnosis of tuberculosis: comparison between HIV-infected and non-HIV-infected patients. *Chest* 1997;111(5):1174–1179.

45. Peterson EM, Nakasone A, Platon-DeLeon JM, Jang Y *et al.* Comparison of direct and concentrated acid-fast smears to identify specimens culture positive for *Mycobacterium* spp. *Journal of Clinical Microbiology* 1999;37(11):3564–3568.

46. Warren JR, Bhattacharya M, De Almeida KN, Trakas K, Peterson LR. A minimum 5.0 ml of sputum improves the sensitivity of acid-fast smear for *Mycobacterium tuberculosis. American Journal of Respiratory & Critical Care Medicine* 2000;161(5):1559–1562.

47. Smith RL, Yew K, Berkowitz KA, Aranda CP. Factors affecting the yield of acid-fast sputum smears in patients with HIV and tuberculosis. *Chest* 1994;106(3):684–686.

48. Ulukanligil M, Aslan G, Tasci S. A comparative study on the different staining methods and number of specimens for the detection of acid fast bacilli. *Memorias do Instituto Oswaldo Cruz* 2000;95(6):855–858.

49. Wilcke JT, Kok-Jensen A. Diagnostic strategy for pulmonary tuberculosis in a low-incidence country: results of chest X-ray and sputum cultured for *Mycobacterium tuberculosis. Respiratory Medicine* 1997; 91(5):281–285.

50. De Villiers RV, Andronikou S, Van de WS. Specificity and sensitivity of chest radiographs in the diagnosis of paediatric pulmonary tuberculosis and the value of additional high-kilovolt radiographs. *Australasian Radiology* 2004;48(2):148–153.

51. Greenberg SD, Frager D, Suster B, Walker S *et al.* Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). *Radiology* 1994;193(1):115–119.

52. Asimos AW, Ehrhardt J. Radiographic presentation of pulmonary tuberculosis in severely immunosuppressed HIV-seropositive patients. *American Journal of Emergency Medicine* 1996;14(4):359–363.

53. Somu N, Swaminathan S, Paramasivan CN, Vijayasekaran D *et al.* Value of bronchoalveolar lavage and gastric lavage in the diagnosis of pulmonary tuberculosis in children. *Tubercle & Lung Disease* 1995;76(4): 295–299.

54. Laven GT. Diagnosis of tuberculosis in children using fluorescence microscopic examination of gastric washings. *American Review of Respiratory Disease* 1977;115(5):743–749.

55. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* 2005;365(9454):130–134.

56. Cowie RL, Langton ME, Escreet BC. Diagnosis of sputum smear- and sputum culture-negative pulmonary tuberculosis. *South African Medical Journal* 1985;68(12):878.

57. A controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 60 months. *American Review of Respiratory Disease* 1984; 130(1):23–28.

58. Nataraj G, Kurup S, Pandit A, Mehta P. Correlation of fine needle aspiration cytology, smear and culture in tuberculous lymphadenitis: a prospective study. *Journal of Postgraduate Medicine* 2002;48(2):113–116.

59. Bekedam HJ, Boeree M, Kamenya A, Liomba G *et al.* Tuberculous lymphadenitis: a diagnostic problem in areas of high prevalence of HIV and tuberculosis. *Transactions of the Royal Society of Tropical Medicine & Hygiene* 1997;91(3):294–297.

60. Lapuerta P, Martin SE, Ellison E. Fine-needle aspiration of peripheral lymph nodes in patients with tuberculosis and HIV. *American Journal of Clinical Pathology* 1997;107(3):317–320.

61. Cutler RR, Baithun SI, Doran HM, Wilson P. Association between the histological diagnosis of tuberculosis and microbiological findings. *Tubercle & Lung Disease* 1994;75(1):75–79.

62. General Medical Council. *Serious communicable diseases.* London: GMC, 1997. (www.gmc-uk.org/guidance/library/serious_communicable_diseases.asp)

63. Public Health (Control of Disease) Act 1984. London: DH, 1984. Available from the The Stationery Office.

64. Drobniewski FA. Diagnosing multidrug resistant tuberculosis in Britain: clinical suspicion should drive rapid diagnosis. *British Medical Journal* 1998;317(7168):1263–1264.

65. Goyal M, Shaw RJ, Banerjee DK, Coker RJ *et al.* Rapid detection of multidrug-resistant tuberculosis. *European Respiratory Journal* 1997;10(5):1120–1124.

66. NHS Health Technology Assessment Programme. *The clinical and cost-effectiveness of diagnostic tests for the detection of mycobacterial infection.* 2004. (**www.ncchta.org/project.asp?PjtId=1247**)

67. Deeks J. 'Systematic reviews of evaluations of diagnostic and screening tests'. In: Egger M, Davey Smith G, Altman D (eds). *Systematic reviews in health care: meta-analysis in context. Second ed. BMJ* 2001;323: 224–228.

68. Joint Tuberculosis Committee of the British Thoracic Society. BTS guidelines: chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998;53(7):536–548.

69. British Thoracic Society. A controlled trial of six months' chemotherapy in pulmonary tuberculosis. Final report: results during the 36 months after the end of chemotherapy and beyond. *British Journal of Diseases of the Chest* 1984;78(4):330–336.

70. Ormerod LP, Horsfield N. Short-course antituberculous chemotherapy for pulmonary and pleural disease: five years' experience in clinical practice. *British Journal of Diseases of the Chest* 1987;81(3): 268–271.

71. Ormerod LP, McCarthy OR, Rudd RM, Horsfield N. Short course chemotherapy for pulmonary tuberculosis. *Respiratory Medicine* 1991;85(4):291–294.

72. Ormerod LP, Prescott RJ. Inter-relations between relapses, drug regimens and compliance with treatment in tuberculosis. *Respiratory Medicine* 1991;85(3):239–242.

73. Nemir RL, Cardona J, Vaziri F, Toledo R. Prednisone as an adjunct in the chemotherapy of lymph node-bronchial tuberculosis in childhood: a double-blind study. II. Further term observation. *American Review of Respiratory Disease* 1967;95(3):402–410.

74. Gelband H. Regimens of less than six months for treating tuberculosis. *The Cochrane Library* 1999;(4):CD001362.

75. Mehrotra ML, Gautam KD, Chaube CK. Shortest possible acceptable, effective ambulatory chemotherapy in pulmonary tuberculosis: preliminary report. *American Review of Respiratory Disease* 1981;124(3):239–244.

76. Santha T, Nazareth O, Krishnamurthy MS, Balasubramanian R *et al.* Treatment of pulmonary tuberculosis with short course chemotherapy in south India-5-year follow up. *Tubercle* 1989;70(4):229–234.

77. Balasubramanian R, Sivasubramanian S, Vijayan VK, Ramachandran R *et al.* Five year results of a three-month and two 5-month regimens for the treatment of sputum-positive pulmonary tuberculosis in south India. *Tubercle* 1990;71(4):253–258.

78. Sputum-smear-negative pulmonary tuberculosis: controlled trial of 3-month and 2-month regimens of chemotherapy. *Lancet* 1979;1(8131):1361–1363.

79. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council.A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis: results at 5 years. *American Review of Respiratory Disease* 1989;139(4): 871–876.

80. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *American Review of Respiratory Disease* 1979;119(4):579–585.

81. Eule H, Beck H, Evers H, Fischer P *et al.* Daily ultrashort chemotherapy and intermittent short-term chemotherapy with 4 drugs of communicable pulmonary tuberculosis treated for the first time: results of a cooperative multicenter study. *Zeitschrift fur Erkrankungen der Atmungsorgane* 1986;167(1–2):29–41.

82. Agarwal SK, Roy DC, Pal D. Once a week short-term tuberculosis therapy. *Asian Medical Journal* 1983; 26(6):390–397.

83. Mwandumba HC, Squire SB. Fully intermittent dosing with drugs for tuberculosis. *The Cochrane Library* 2001;(4).

84. Mitchison DA, Aber V, Allen BW. Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. *Lancet* 1981;1(8213):171–174.

85. Castelo A, Jardim JR, Goihman S, Kalckman AS *et al.* Comparison of daily and twice-weekly regimens to treat pulmonary tuberculosis. *Lancet* 1989;2(8673):1173–1176.

86. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet* 2004;364(9441):1244–1251.

87. Zierski M, Bek E, Long MW, Snider DE, Jr. Short-course (6 month) cooperative tuberculosis study in Poland: results 18 months after completion of treatment. *American Review of Respiratory Disease* 1980; 122(6):879–889.

88. Prasad R, Garg R, Mukerji PK, Jain A. Comparative study of daily and thrice weekly intermittent regimens given for six months in the treatment of pulmonary tuberculosis. *Journal of Internal Medicine of India* 2001;4(1):1–3.

89. Alwood K, Keruly J, Moore-Rice K, Stanton DL *et al.* Effectiveness of supervised, intermittent therapy for tuberculosis in HIV-infected patients. *AIDS* 1994;8(8):1103–1108.

90. Naude JMTW, Donald PR, Hussey GD, Kibel MA *et al.* Twice weekly vs. daily chemotherapy for childhood tuberculosis. *Pediatric Infectious Disease Journal* 2000;19(5):405–410.

91. Geiter LJ, O'Brien RJ, Combs DL, Snider DE, Jr. United States Public Health Service Tuberculosis Therapy Trial 21: preliminary results of an evaluation of a combination tablet of isoniazid, rifampin and pyrazinamide. *Tubercle* 1987;68(2 Suppl):41–46.

92. Girling DJ, Chan SL. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide: results at 30 months. *American Review of Respiratory Disease* 1991;143(4 I):700–706.

93. Zhang LX, Kan GQ, Tu DH, Wan LY, Faruqi AR. Fixed-dose combination chemotherapy versus multiple, single-drug chemotherapy for tuberculosis. *Current Therapeutic Research Clinical and Experimental* 1996;57:849–856.

94. Teo SK. Assessment of a combined preparation of isoniazid, rifampicin and pyrazinamide (Rifater) in the initial phase of chemotherapy in three 6-month regimens for smear-positive pulmonary tuberculosis: a five-year follow-up report. *International Journal of Tuberculosis & Lung Disease* 1999;3(2):126–132.

95. Su WJ, Perng RP. Fixed-dose combination chemotherapy (Rifater/Rifinah) for active pulmonary tuberculosis in Taiwan: a two-year follow-up. *International Journal of Tuberculosis & Lung Disease* 2002;6(11):1029–1032.

96. Gravendeel JMT, Asapa AS, Becx-Bleumink M, Vrakking HA. Preliminary results of an operational field study to compare side-effects, complaints and treatment results of a single-drug short-course regimen with a four-drug fixed-dose combination (4FDC) regimen in South Sulawesi, Republic of Indonesia. *Tuberculosis* 2003;83(1–3):183–186.

97. Ormerod LP, Bentley C. The management of lymph node tuberculosis notified in England and Wales in 1993. *Journal of the Royal College of Physicians of London* 1997;31(6):666–668.

98. Ormerod LP, Bentley C. The management of pulmonary tuberculosis notified in England and Wales in 1993. *Journal of the Royal College of Physicians of London* 1997;31(6):662–665.

99. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *American Review of Respiratory Disease* 1986;133(3):423–430.

100. Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. *Morbidity & Mortality Weekly Report* 2002;51(10):214–215.

101. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *American Review of Respiratory Disease* 1980;121(6):939–949.

102. Rouillon A, Perdrizet S, Parrot R. Transmission of tubercle bacilli: the effects of chemotherapy. *Tubercle* 1976;57(4):275–299.

103. Tokars JI, McKinley GF, Otten J, Woodley C *et al.* Use and efficacy of tuberculosis infection control practices at hospitals with previous outbreaks of multidrug-resistant tuberculosis. *Infection Control & Hospital Epidemiology* 2001;22(7):449–455.

104. Health and Safety Executive. *Respiratory protective equipment at work: a practical guide.* London: HSE, 2005.

105. NHS Estates. *Isolation facilities in acute settings: in patient accommodation: options for choice.* Health Building Notes 4 supplement 1. London, 2005.

106. Wallgren A. The timetable of tuberculosis. *Tubercle* 1948;29:245–251.

107. Ormerod LP, Horsfield N. Miliary tuberculosis in a high prevalence area of the United Kingdom. Blackburn 1978–93. *Respiratory Medicine* 1995;89(8):555–557.

108. MRC Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment in tuberculous meningitis. *Lancet* 1947;1:582–597.

109. Teoh R, Humphries MJ, O'Mahoney G. Symptomatic intracranial tuberculoma developing during treatment of tuberculosis: a report of 10 cases and a review of the literature. *Quarterly Journal of Medicine* 1987;63(241):449–460.

110. Martineau AR, Lowey H, Tocque K, Davies PD. Decreasing tuberculosis case fatality in England and Wales, 1988–2001. *International Journal of Tuberculosis & Lung Disease* 2004;8(6):737–742.

111. Doganay M, Calangu S, Turgut H, Bakir M, Aygen B. Treatment of tuberculous meningitis in Turkey. *Scandinavian Journal of Infectious Diseases* 1995;27(2):135–138.

112. *Short-course chemotherapy for tuberculous meningitis.* 89 A.D. Oct 22; the XIVth World Congress of Neurology. 1990.

113. Chotmongkol V. Treatment of tuberculous meningitis with 6-month course of chemotherapy. *Southeast Asian Journal of Tropical Medicine & Public Health* 1991;22(3):372–374.

114. Alarcon F, Escalante L, Perez Y, Banda H*et al.* Tuberculous meningitis: short course of chemotherapy. *Archives of Neurology* 1990;47(12):1313–1317.

115. Acharya VN, Kudva BT, Retnam VJ, Mehta PJ. Adult tuberculous meningitis: comparative study of different chemotherapeutic regimens. *Journal of the Association of Physicians of India* 1985;33(9):583–585.

116. Loenhout-Rooyackers JH, Keyser A, Laheij RJ, Verbeek AL, van der Meer JW. Tuberculous meningitis: is a 6-month treatment regimen sufficient? *International Journal of Tuberculosis & Lung Disease* 2001; 5(11):1028–1035.

117. Jacobs RF, Sunakorn P, Chotpitayasunonah T, Pope S, Kelleher K. Intensive short course chemotherapy for tuberculous meningitis. *Pediatric Infectious Disease Journal* 1992;11(3):194–198.

118. Donald PR, Schoeman JF, Van Zyl LE, De Villiers JN *et al.* Intensive short course chemotherapy in the management of tuberculous meningitis. *International Journal of Tuberculosis & Lung Disease* 1998; 2(9):704–711.

119. Phuapradit P, Vejjajiva A. Treatment of tuberculous meningitis: role of short-course chemotherapy. *Quarterly Journal of Medicine* 1987;62(239):249–258.

120. Goel A, Pandya SK, Satoskar AR. Whither short-course chemotherapy for tuberculous meningitis? *Neurosurgery* 1990;27(3):418–421.

121. Humphries MJ, Teoh R, Lau J, Gabriel M. Factors of prognostic significance in Chinese children with tuberculous meningitis. *Tubercle* 1990;71(3):161–168.

122. Ramachandran P, Duraipandian M, Nagarajan M, Prabhakar R *et al.* Three chemotherapy studies of tuberculous meningitis in children. *Tubercle* 1986;67(1):17–29.

123. Ramachandran P, Duraipandian M, Reetha AM, Mahalakshmi SM, Prabhakar R. Long-term status of children treated for tuberculous meningitis in south India. *Tubercle* 1989;70(4):235–239.

124. Prasad K, Volmink J, Menon GR. Steroids for treating tuberculous meningitis. *The Cochrane Library* 2000;(3):CD002244.

125. O'Toole RD, Thornton GF, Mukherjee MK, Nath RL. Dexamethasone in tuberculous meningitis: relationship of cerebrospinal fluid effects to therapeutic efficacy. *Annals of Internal Medicine* 1969; 70(1):39–48.

126. Girgis NI, Farid Z, Kilpatrick ME, Sultan Y, Mikhail IA. Dexamethasone adjunctive treatment for tuberculous meningitis. *Pediatric Infectious Disease Journal* 1991;10(3):179–183.

127. Kumarvelu S, Prasad K, Khosla A, Behari M, Ahuja GK. Randomized controlled trial of dexamethasone in tuberculous meningitis. *Tubercle & Lung Disease* 1994;75(3):203–207.

128. Chotmongkol V, Jitpimolmard S, Thavornpitak Y. Corticosteroid in tuberculous meningitis. *Journal of the Medical Association of Thailand* 1996;79(2):83–90.

129. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics* 1997;99(2):226–231.

130. Lardizabal DV, Roxas AA. Dexamethasone as adjunctive therapy in adult patients with probable tuberculous meningitis stage II and IH: an open randomized controlled trial. *The Philippine Journal of Neurology* 1998;4:2–11.

131. Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroid therapy for tuberculosis: *a* critical reappraisal of the literature. *Clinical Infectious Diseases* 1997;25(4):872–887.

132. Thwaites GE, Nguyen HD, Hoang TQ, Do TT, Nguyen TC. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *New England Journal of Medicine* 2004;351(17): 1741–1751.

133. Ormerod LP. Tuberculosis in pregnancy and the puerperium. *Thorax* 2001;56(6):494–499.

134. Campbell IA, Dyson AJ. Lymph node tuberculosis: *a* comparison of various methods of treatment. *Tubercle* 1977;58(4):171–179.

135. British Thoracic Society Research Committee. Short course chemotherapy for tuberculosis of lymph nodes: a controlled trial. *British Medical Journal* (Clinical research ed) 1985;290(6475):1106–1108.

136. British Thoracic Society Research Committee. Six-months versus nine-months chemotherapy for tuberculosis of lymph nodes: preliminary results. *Respiratory Medicine* 1992;86(1):15–19.

137. Campbell IA, Ormerod LP, Friend JA, Jenkins PA, Prescott RJ. Six months versus nine months chemotherapy for tuberculosis of lymph nodes: final results. *Respiratory Medicine* 1993;87(8):621–623.

138. Loenhout-Rooyackers JH, Laheij RJ, Richter C, Verbeek AL. Shortening the duration of treatment for cervical tuberculous lymphadenitis. *European Respiratory Journal* 2000;15(1):192–195.

139. Yuen AP, Wong SH, Tam CM, Chan SL *et al.* Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy. *Otolaryngology – Head & Neck Surgery* 1997;116(2):189–192.

140. Tuberculosis Section: Health Protection Agency Centre for Infections. *Annual report on tuberculosis cases reported in 2002 in England, Wales and Northern Ireland: enhanced tuberculosis surveillance.* London: Health Protection Agency, 2005.

141. Upadhyay SS, Saji MJ, Yau AC. Duration of antituberculosis chemotherapy in conjunction with radical surgery in the management of spinal tuberculosis. *Spine* 1996;21(16):1898–1903.

142. Medical Research Council Working Party on tuberculosis of the spine Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. *International Orthopaedics* 1999;23(2):73–81.

143. Parthasarathy R, Sriram K, Santha T, Prabhakar R *et al.* Short-course chemotherapy for tuberculosis of the spine: a comparison between ambulant treatment and radical surgery – ten-year report. *Journal of Bone & Joint Surgery British Volume* 1999;81B(3):464–471.

144. Medical Research Council Working Party on Tuberculosis of the Spine. A controlled trial of ambulant outpatient treatment and in-patient rest in bed in the management of tuberculosis of the spine in young Korean patients on standard chemotherapy. *Journal of Bone & Joint Surgery British Volume* 1973;55B(4): 678–697.

145. Medical Research Council Working Party on Tuberculosis of the Spine. A 5-year assessment of controlled trials of inpatient and outpatient treatment and of plaster-of-paris jackets for tuberculosis of the spine in children on standard chemotherapy. *Journal of Bone & Joint Surgery British Volume* 1976;58B(4): 399–411.

146. Medical Research Council Working Party on Tuberculosis of the Spine. A controlled trial of plaster-of-paris jackets in the management of ambulatory outpatient treatment of tuberculosis of the spine in children on standard chemotherapy: a study in Pusan, Korea. *Tubercle* 1973;54(4):261–282.

147. Medical Research Council Working Party. A controlled trial of debridement and ambulatory treatment in the management of tuberculosis of the spine in patients on standard chemotherapy: *a* study in Bulawayo, Rhodesia. *Journal of Tropical Medicine & Hygiene* 1974;77(4):72–92.

148. Medical Research Council Working Party on tuberculosis of the spine. A controlled trial of anterior spinal fusion and debridement in the surgical management of tuberculosis of the spine in patients on standard chemotherapy: *a* study in two centres in South Africa. *Tubercle* 1978;59(2):79–105.

149. Medical Research Council Working Party on Tuberculosis of the Spine. Five-year assessments of controlled trials of ambulatory treatment, debridement and anterior spinal fusion in the management of tuberculosis of the spine: studies in Bulawayo (Rhodesia) and in Hong Kong. *Journal of Bone & Joint Surgery British Volume* 1978;60B(2):163–177.

150. Medical Research Council Working Party on Tuberculosis of the Spine. A controlled trial of anterior spinal fusion and debridement in the surgical management of tuberculosis of the spine in patients on standard chemotherapy: a study in two centres in South Africa. *Tubercle* 1978;59(2):79–105.

151. Griffiths DL, Seddon H, Ball J, Darbyshire J *et al.* A controlled trial of short-course regimens of chemotherapy in patients receiving ambulatory treatment or undergoing radical surgery for tuberculosis of the spine. *Indian Journal of Tuberculosis* 1989;36(2 SUPPL.).

152. Strang JI, Kakaza HH, Gibson DG, Girling DJ *et al.* Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet* 1987;2(8573):1418–1422.

153. Strang JIG, Karaza HHS, Gibson DG, Allen BW *et al.* Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet* 1988;2(8614):759–764.

154. Mayosi BM, Ntsekhe M, Volmink JA, Commerford P. Interventions for treating tuberculous pericarditis. *The Cochrane Library* 2002;(4).

155. Ntsekhe M, Wiysonge C, Volmink JA, Commerford PJ, Mayosi BM. Adjuvant corticosteroids for tuberculous pericarditis: promising, but not proven. *Monthly Journal of the Association of Physicians* 2003;96(8):593–599.

156. Schrire V. Experience with pericarditis at Groote Schuur Hospital, Cape Town: an analysis of one hundred and sixty cases studied over a six-year period. *South African Medical Journal* 1959;33:810–817.

157. Hakim JG, Ternouth I, Mushangi E, Siziya S *et al.* Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart* 2000;84(2):183–188.

158. Strang JIG. Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. *Quarterly Journal of Medicine* 2004;97(8):525–535.

159. Anadol D, Kiper N, Gocmen A, Ozcelik U. Intermittent chemotherapy for miliary tuberculosis in children. *Turkish Journal of Pediatrics* 1999;41(1):53–59.

160. Ormerod LP, Green RM, Horsfield N. Tuberculosis treatment outcome monitoring: Blackburn 1988–2000. *International Journal of Tuberculosis & Lung Disease* 2002;6(8):662–665.

161. Hayden SP, Springett VH. An assessment of the place of follow-up pulmonary tuberculosis. *British Journal of Diseases of the Chest* 1978;72(3):217–221.

162. Pearce SJ, Horne NW. Follow-up of patients with pulmonary tuberculosis adequately treated by chemotherapy: is this really necessary? *Lancet* 1974;2(7881):641–643.

163. Bailey WC, Thompson DH, Jacobs S, Ziskind M, Greenberg HB. Evaluating the need for periodic recall and re-examination of patients with inactive pulmonary tuberculosis. *American Review of Respiratory Disease* 1973;107(5):854–857.

164. Edsall J, Collins G. Routine follow-up of inactive tuberculosis, a practice to be abandoned. *American Review of Respiratory Disease* 1973;107(5):850–853.

165. Pamra SP, Prasad G, Mathur GP. Relapse in pulmonary tuberculosis. *American Review of Respiratory Disease* 1976;113(1):67–72.

166. World Health Organization. *Global tuberculosis control: surveilance, planning, financing.* Switzerland: World Health Organization, 2004.

167. Bayer R, Stayton C, Desvarieux M, Healton C *et al.* Directly observed therapy and treatment completion for tuberculosis in the United States: is universal supervised therapy necessary? *American Journal of Public Health* 1998;88(7):1052–1058.

168. Garner P. What makes DOT work? Directly observed therapy. *Lancet* 1998;352(9137):1326–1327.

169. Garner P, Volmink J. Directly observed therapy (letter). *Lancet* 1997;350(9078):666–667.

170. Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of pulmonary tuberculosis: consensus statement of the Public Health Tuberculosis Guidelines Panel. *Journal of the American Medical Association* 1998;279(12):943–948.

171. Hill AR, Manikal VM, Riska PF. Effectiveness of directly observed therapy (DOT) for tuberculosis: a review of multinational experience reported in 1990–2000. *Medicine* 2002;81(3):179–193.

172. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *The Cochrane Library* 2003;(1).

173. MacIntyre CR, Goebel K, Brown GV, Skull S *et al.* A randomised controlled clinical trial of the efficacy of family-based direct observation of anti-tuberculosis treatment in an urban, developed-country setting. *International Journal of Tuberculosis & Lung Disease* 2003;7(9):848–854.

174. Matteelli A, Casalini C, Raviglione MC, El Hamad I *et al.* Supervised preventive therapy for latent tuberculosis infection in illegal immigrants in Italy. *American Journal of Respiratory & Critical Care Medicine* 2000;162(5):1653–1655.

175. Tandon M. DOTS versus self administered therapy (SAT) for patients of pulmonary tuberculosis: a randomised trial at a tertiary care hospital. *Indian Journal of Medical Sciences* 2002;56(1):19–21.

176. Tulsky JP, Pilote L, Hahn JA, Zolopa AJ *et al.* Adherence to isoniazid prophylaxis in the homeless: a randomized controlled trial. *Archives of Internal Medicine* 2000;160(5):697–702.

177. Chaulk P, Kazandjian VA. Comprehensive case management models for pulmonary tuberculosis. *Disease Management & Health Outcomes* 2003;11(9):571–577.

178. Kamolratanakul P. Randomized controlled trial of directly observed treatment (DOT) for patients with pulmonary tuberculosis in Thailand. *Transactions of the Royal Society of Tropical Medicine & Hygiene* 1999;93(5):552–557.

179. Walley JD, Khan MA, Newell JN, Khan MH. Effectiveness of the direct observation component of DOTS for tuberculosis: *a* randomised controlled trial in Pakistan. *Lancet* 2001;357(9257):664–669.

180. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. *Lancet* 1998;352(9137):1340–1343.

181. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. A randomised controlled trial of lay health workers as direct observers for treatment of tuberculosis. *International Journal of Tuberculosis & Lung Disease* 2000;4(6):550–554.

182. Malotte CK, Hollingshead JR, Larro M. Incentives vs outreach workers for latent tuberculosis treatment in drug users. *American Journal of Preventive Medicine* 2001;20(2):103–107.

183. Chaisson RE, Barnes GL, Hackman J, Watkinson L *et al.* A randomized, controlled trial of interventions to improve adherence to isoniazid therapy to prevent tuberculosis in injection drug users. *American Journal of Medicine* 2001;110(8):610–615.

184. Wandwalo E, Kapalata N, Egwaga S, Morkve O. Effectiveness of community-based directly observed treatment for tuberculosis in an urban setting in Tanzania: a randomised controlled trial. *International Journal of Tuberculosis & Lung Disease* 2004;8(10):1248–1254.

185. Lwilla F, Schellenberg D, Masanja H, Acosta C *et al.* Evaluation of efficacy of community-based vs. institutional-based direct observed short-course treatment for the control of tuberculosis in Kilombero district, Tanzania. *Tropical Medicine & International Health* 2003;8(3):204–210.

186. Wright J, Walley J, Philip A, Pushpananthan S *et al.* Direct observation of treatment for tuberculosis: a randomized controlled trial of community health workers versus family members. *Tropical Medicine & International Health* 2004;9(5):559–565.

187. Mullen PD. Compliance becomes concordance. *British Medical Journal* 1997;314(7092):691–692

188. Ormerod LP. Management of pulmonary and lymph node tuberculosis notified in 1998 in England and Wales. *Clinical Medicine* 2003;3(1):57–61.

189. Fox W. Compliance of patients and physicians: experience and lessons from tuberculosis (I). *British Medical Journal* 1983;287(6384):33–35.

190. Fox W. Compliance of patients and physicians: experience and lessons from tuberculosis (II). *British Medical Journal* 1983;287(6385):101–105.

191. Volmink J, Garner P. Systematic review of randomised controlled trials of strategies to promote adherence to tuberculosis treatment. *British Medical Journal* 1997;315(7120):1403–1406.

192. Jin BW, Kim SC, Mori T, Shimao T. The impact of intensified supervisory activities on tuberculosis treatment. *Tubercle & Lung Disease* 1993;74(4):267–272.

193. Paramasivan R, Parthasarathy RT, Rajasekaran S. Short course chemotherapy: a controlled study of indirect defaulter retrieval method. *Indian Journal of Tuberculosis* 1993;40:185–190.

194. Pilote L, Tulsky JP, Zolopa AR, Hahn JA *et al.* Tuberculosis prophylaxis in the homeless: a trial to improve adherence to referral. *Archives of Internal Medicine* 1996;156(2):161–165.

195. Salleras SL, Alcaide MJ, Altet GMN, Canela SJ *et al.* Evaluation of the efficacy of health education on the compliance with antituberculosis chemoprophylaxis in school children: a randomized clinical trial. *Tubercle & Lung Disease* 1993;74(1):28–31.

196. Morisky DE, Malotte CK, Choi P *et al.* A patient education program to improve adherence rates with antituberculosis drug regimens. *Health Education Quarterly* 1990;17(3):253–267.

197. Krishnaswami KV, Somasundaram PR, Tripathy SP, Vaidyanathan B *et al.* A randomised study of two policies for managing default in out-patients collecting supplies of drugs for pulmonary tuberculosis in a large city in south India. *Tubercle* 1981;62(2):103–112.

198. Liefooghe R, Suetens C, Meulemans H, Moran MB, De Muynck A. A randomised trial of the impact of counselling on treatment adherence of tuberculosis patients in Sialkot, Pakistan. *International Journal of Tuberculosis & Lung Disease* 1999;3(12):1073–1080.

199. Moulding TS, Caymittes M. Managing medication compliance of tuberculosis patients in Haiti with medication monitors. *International Journal of Tuberculosis & Lung Disease* 2002;6(4):313–319.

200. Dick J, Lombard C. Shared vision-a health education project designed to enhance adherence to anti-tuberculosis treatment. *International Journal of Tuberculosis & Lung Disease* 1997;1(2):181–186.

201. Bock NN, Sales RM, Rogers T, DeVoe B. A spoonful of sugar...: improving adherence to tuberculosis treatment using financial incentives. *International Journal of Tuberculosis & Lung Disease* 2001;5(1):96–98.

202. Davidson H, Schluger NW, Feldman PH, Valentine DP *et al.* The effects of increasing incentives on adherence to tuberculosis directly observed therapy. *International Journal of Tuberculosis & Lung Disease* 2000;4(9):860–865.

203. Barnwell MD, Chitkara R, Lamberta F. Tuberculosis prevention project. *Journal of the National Medical Association* 1992;84(12):1014–1018.

204. Hovell MF, Sipan CL, Blumberg EJ, Hofstetter CR *et al.* Increasing Latino adolescents' adherence to treatment for latent tuberculosis infection: a controlled trial. *American Journal of Public Health* 2003;93(11):1871–1877.

205. Morisky DE, Malotte CK, Ebin V, Davidson P *et al.* Behavioral interventions for the control of tuberculosis among adolescents. *Public Health Reports* 2001;116(6):568–574.

206. White MC, Tulsky JP, Reilly P, McIntosh HW *et al.* A clinical trial of a financial incentive to go to the tuberculosis clinic for isoniazid after release from jail. *International Journal of Tuberculosis & Lung Disease* 1998;2(6):506–512.

207. Tulsky JP, Hahn JA, Long HL, Chambers DB *et al.* Can the poor adhere? Incentives for adherence to TB prevention in homeless adults. *International Journal of Tuberculosis & Lung Disease* 2004;8(1):83–91.

208. White MC, Tulsky JP, Goldenson J, Portillo CJ *et al.* Randomized controlled trial of interventions to improve follow-up for latent tuberculosis infection after release from jail. *Archives of Internal Medicine* 2002;162(9):1044–1050.

209. British Thoracic Association. A controlled trial of six months chemotherapy in pulmonary tuberculosis. First Report: results during chemotherapy. *British Journal of Diseases of the Chest* 1981;75(2):141–153.

210. Veen J, Raviglione M, Rieder HL, Migliori GB *et al.* Standardized tuberculosis treatment outcome monitoring in Europe: recommendations of a Working Group of the World Health Organization (WHO) and the European Region of the International Union Against Tuberculosis and Lung Disease (IUATLD) for uniform reporting by cohort analysis of treatment outcome in tuberculosis patients. *European Respiratory Journal* 1998;12(2):505–510.

211. White VLC, Moore-Gillon J. Resource implications of patients with multidrug resistant tuberculosis. *Thorax* 2000;55(11):962–963.

212. World Health Organization. *Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-Tuberculosis Dug Resistance Surveillance.* Geneva: World Health Organization, 2004.

213. Djuretic T, Herbert J, Drobniewski F, Yates M *et al.* Antibiotic resistant tuberculosis in the United Kingdom:1993–1999. *Thorax* 2002;57(6):477–482.

214. Al Jarad N, Parastatides S, Paul EA, Sheldon CD *et al.* Characteristics of patients with drug resistant and drug sensitive tuberculosis in East London between 1984 and 1992. *Thorax* 1994;49(8):808–810.

215. Pritchard AJ, Hayward AC, Monk PN, Neal KR. Risk factors for drug resistant tuberculosis in Leicestershire-poor adherence to treatment remains an important cause of resistance. *Epidemiology & Infection* 2003;130(3):481–483.

216. Conaty SJ, Hayward AC. Explaining risk factors for drug resistant tuberculosis in England and Wales: contribution of primary and secondary drug resistance. *Epidemiology & Infection* 2004;132:1099–1108.

217. Anastasis D, Pillai G, Rambiritch V, Abdool Karim SS. A retrospective study of human immunodeficiency virus infection and drug-resistant tuberculosis in Durban, South Africa. *International Journal of Tuberculosis & Lung Disease* 1997;1(3):220–224.

218. Githui WA, Juma ES, Van Gorkom J, Kibuga D *et al.* Antituberculosis drug resistance surveillance in Kenya, 1995. *International Journal of Tuberculosis & Lung Disease* 1998;2(6):499–505.

219. Weyer K, Groenewald P, Zwarenstein M, Lombard CJ. Tuberculosis drug resistance in the Western Cape. *South African Medical Journal* 1995;85(6):499–504.

220. Wilkinson D, Pillay M, Davies GR, Sturm AW. Resistance to antituberculosis drugs in rural South Africa: rates, patterns, risks, and transmission dynamics. *Transactions of the Royal Society of Tropical Medicine & Hygiene* 1996;90(6):692–695.

221. Moore M, Onorato IM, McCray E, Castro KG. Trends in drug-resistant tuberculosis in the United States, 1993–1996. *Journal of the American Medical Association* 1997;278(10):833–837.

222. Robert J, Trystram D, Truffot-Pernot C, Carbonnelle B, Grosset J. Surveillance of *Mycobacterium tuberculosis* drug resistance in France, 1995–1997. AZAY Mycobacteria Study Group. *International Journal of Tuberculosis & Lung Disease* 2000;4(7):665–672.

223. Lambregts-Van Weezenbeek CSB, Jansen HM, Nagelkerke NJD, Van Klingeren B, Veen J. Nationwide surveillance of drug-resistant tuberculosis in the Netherlands: rates, risk factors and treatment outcome. *International Journal of Tuberculosis & Lung Disease* 1998;2(4):288–295.

224. Helbling P, Altpeter E, Raeber PA, Pfyffer GE, Zellweger JP. Surveillance of antituberculosis drug resistance in Switzerland 1995–1997: the central link. *European Respiratory Journal* 2000;16(2):200–202.

225. Sharma SK, Turaga KK, Balamurugan A, Saha PK *et al.* Clinical and genetic risk factors for the development of multi-drug resistant tuberculosis in non-HIV infected patients at a tertiary care center in India: a case-control study. *Infection, Genetics & Evolution* 2003;3(3):183–188.

226. Salomon N, Perlman DC, Friedmann P, Buchstein S *et al.* Predictors and outcome of multidrug-resistant tuberculosis. *Clinical Infectious Diseases* 1995;21(5):1245–1252.

227. Goble M, Iseman MD, Madsen LA, Waite D *et al.* Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *New England Journal of Medicine* 1993;328(8):527–532.

228. Telzak EE, Sepkowitz K, Alpert P, Mannheimer S *et al.* Multidrug-resistant tuberculosis in patients without HIV infection. *New England Journal of Medicine* 1995;333(14):907–911.

229. Herrera D. Multidrug-resistant tuberculosis outbreak on an HIV ward-Madrid, Spain, 1991–1995. *Morbidity & Mortality Weekly Report* 1996;45(16):330–333.

230. Chan ED, Laurel V, Strand MJ, Chan JF *et al.* Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *American Journal of Respiratory & Critical Care Medicine* 2004;169(10): 1103–1109.

231. Narita M, Alonso P, Lauzardo M, Hollender ES *et al.* Treatment experience of multidrug-resistant tuberculosis in Florida, 1994–1997. *Chest* 2001;120(2):343–348.

232. Breathnach AS, de Ruiter A, Holdsworth GM, Bateman NT *et al.* An outbreak of multi-drug-resistant tuberculosis in a London teaching hospital. *Journal of Hospital Infection* 1998;39(2):111–117.

233. Maloney SA, Pearson ML, Gordon MT, Del Castillo R *et al.* Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. *Annals of Internal Medicine* 1995;122(2):90–95.

234. Stroud LA, Tokars JI, Grieco MH, Crawford JT *et al.* Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* in a New York City hospital. *Infection Control & Hospital Epidemiology* 1995;16(3):141–147.

235. Wenger PN, Otten J, Breeden A, Orfas D *et al.* Control of nosocomical transmission of multidrug-resistant *Mycobacterium tuberculosis* among healthcare workers and HIV-infected patients. *Lancet* 1995;345(8944):235–240.

236. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *The Cochrane Library* 1999;(1).

237. Girling DJ, Chan SL. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *American Review of Respiratory Disease* 1992;145:36–41.

238. Thompson NJ. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. *Bulletin of the World Health Organization* 1982;60(4):555–564.

239. Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL *et al.* Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Annals of Internal Medicine* 2002;137(8):640–647.

240. McNeill L, Allen M, Estrada C, Cook P. Pyrazinamide and rifampin vs isoniazid for the treatment of latent tuberculosis: improved completion rates but more hepatotoxicity. *Chest* 2003;123(1):102–106.

241. Leung CC, Law WS, Chang KC, Tam CM *et al.* Initial experience on rifampin and pyrazinamide vs isoniazid in the treatment of latent tuberculosis infection among patients with silicosis in Hong Kong. *Chest* 2003;124(6):2112–2118.

242. Gupta DK, Kumar R, Nath N, Kothari AK. Chemoprophylaxis in high risk children-analysis of 8 years' follow up: preliminary report. *Indian Journal of Tuberculosis* 1993;40:125–127.

243. Ormerod LP. Rifampicin and isoniazid prophylactic chemotherapy for tuberculosis. *Archives of Disease in Childhood* 1998;78(2):169–171.

244. Bucher HC, Griffith LE, Guyatt GH, Sudre P *et al.* Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. *AIDS* 1999;13(4):501–507.

245. Wilkinson D, Squire SB, Garner P. Effect of preventive treatment for tuberculosis in adults infected with HIV: systematic review of randomised placebo controlled trials. *British Medical Journal* 1998;317(7159):625–629.

246. Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *The Cochrane Library* 2004;(1):CD0001171.

247. Wilkinson D. Drugs for preventing tuberculosis in HIV infected persons. *The Cochrane Library* 2000;(4).

248. American Thoracic Society and the Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *American Journal of Respiratory & Critical Care Medicine* 2000;161(4 Pt 2):S221–S247.

249. Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection – New York and Georgia, 2000. *Morbidity & Mortality Weekly Report* 2001;50(15):289–291.

250. American Thoracic Society and the Centers for Disease Control and Prevention. Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection *Morbidity & Mortality Weekly Report* 2001;50(34):733–735.

251. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *International Journal of Tuberculosis & Lung Disease* 2002;6(11):995–1000.

252. Enarson DA. 'The epidemiological basis of tuberculosis control'. In: *Clinical tuberculosis.* London, Chapman & Hall, 1998.

253. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *Journal of the American Medical Association* 1999;282(7):677–686.

254. Cohn DL, El Sadr WM. 'Treatment of latent tuberculosis infection'. In: *Tuberculosis: a comprehensive international approach. Second ed.* New York: Marcel Dekker, 2000.

255. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE *et al.* A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *New England Journal of Medicine* 1989;320(9):545–550.

256. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis: a general review. *Bibliotheca Tuberculosea* 1970;26:28–106.

257. Sutherland I, Svandova E, Radhakrishna S. The development of clinical tuberculosis following infection with tubercle bacilli. *Tubercle* 1982;63(4):255–268.

258. Falk A, Fuchs GF. Prophylaxis with isoniazid in inactive tuberculosis: a veterans administration cooperative study XII. *Chest* 1978;73(1):44–48.

259. Steinbruck P, Dankova D, Edwards LB, Doster B, Livesay VT. The risk of tuberculosis in patients with fibrous lesions radiologically diagnosed [French]. *Bulletin of the International Union Against Tuberculosis* 1972;47:144–171.

260. Palmer C, Jablon S, Edwards P. Tuberculosis morbidity of young men in relation to tuberculin sensitivity and body build. *American Review of Tuberculosis* 1957;76(4):517–539.

261. Lichtenstein IH, MacGregor RR. Mycobacterial infections in renal transplant recipients: report of five cases and review of the literature. *Review of Infectious Diseases* 1983;5(2):216–226.

262. Munoz P, Palomo J, Munoz R, Rodriguez-Creixems M *et al.* Tuberculosis in heart transplant recipients. *Clinical Infectious Diseases* 1995;21(2):398–402.

263. Korner MM, Hirata N, Tenderich G, Minami K *et al.* Tuberculosis in heart transplant recipients. *Chest* 1997;111(2):365–369.

264. Pickleman JR, Evans LS, Kane JM, Freeark RJ. Tuberculosis after jejunoileal bypass for obesity. *Journal of the American Medical Association* 1975;234(7):744.

265. Bruce RM, Wise L. Tuberculosis after jejunoileal bypass for obesity. *Annals of Internal Medicine* 1977;87(5):574–576.

266. Paul R. Silicosis in Northern Rhodesia copper miners. *Archives of Environmental Health* 1961;2:96–109.

267. Lundin AP, Adler AJ, Berlyne GM, Friedman EA. Tuberculosis in patients undergoing maintenance hemodialysis. *American Journal of Medicine* 1979;67(4):597–602.

268. Chia S, Karim M, Elwood RK, FitzGerald JM. Risk of tuberculosis in dialysis patients: a population-based study. *International Journal of Tuberculosis & Lung Disease* 1998;2(12):989–991.

269. Andrew OT, Schoenfeld PY, Hopewell PC, Humphreys MH. Tuberculosis in patients with end-stage renal disease. *American Journal of Medicine* 1980;68(1):59–65.

270. Thorn P, Brookes V, Waterhouse J. Peptic ulcer, partial gastrectomy, and pulmonary tuberculosis. *British Medical Journal* 1956;(4967):603–608.

271. Snider DE. Tuberculosis and gastrectomy. *Chest* 1985;87(4):414–415.

272. Steiger Z, Nickel WO, Shannon GJ, Nedwicki EG, Higgins RF. Pulmonary tuberculosis after gastric resection. *American Journal of Surgery* 1976;131(6):668–671.

273. Pablos-Mendez A, Blustein J, Knirsch CA. The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. *American Journal of Public Health* 1997;87(4):574–579.

274. Boucot K, Dillon E, Cooper D, Meier P, Richardson R. Tuberculosis among diabetics: the Philadelphia survey. *American Review of Tuberculosis* 1952;65(1:2):1–50.

275. Oscarsson PN, Silwar H. Incidence of pulmonary tubereculosis among diabetics: search among diabetics in the county of Kristianstad. *Acta Medica Scandinavia* 1958;161(Suppl 335):23–48.

276. Keane J, Gershon S, Wise RP, Mirabile-Levens E *et al.* Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *New England Journal of Medicine* 2001;345(15):1098–1104.

277. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis & Rheumatism* 2004;50(2):372–379.

278. The British Thoracic Association. A study of a standardised contact procedure in tuberculosis. *Tubercle* 1978;59(4):245–259.

279. Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. *Bulletin of the World Health Organization* 1990;68(1):93–108.

280. Fine PE. Bacille Calmette-Guerin vaccines: a rough guide. *Clinical Infectious Diseases* 1995;20(1):11–14.

281. Wilson ME, Fineberg HV, Colditz GA. Geographic latitude and the efficacy of bacillus Calmette-Guerin vaccine. *Clinical Infectious Diseases* 1995;20(4):982–991.

282. Trial of BCG vaccines in south India for tuberculosis prevention: first report – Tuberculosis Prevention Trial. *Bulletin of the World Health Organization* 1979;57(5):819–827.

283. Packe GE, Innes JA. Protective effect of BCG vaccination in infant Asians: a case control study. *Archives of Disease in Childhood* 1988;63(3):277–281.

284. Hart PD, Surtherland I, Thomas J. The immunity conferred by effective BCG and vole bacillus vaccines, in relation to individual variations in induced tuberculin sensitivity and to technical variations in the vaccines. *Tubercle* 1967;48:201–210.

285. Hart PD, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life: final report to the Medical Research Council. *British Medical Journal* 1977;2(6082):293–295.

286. Aronson NE, Santosham M, Comstock GW, Howard RS *et al.* Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: a 60-year follow-up study. *Journal of the American Medical Association* 2004;291(17):2086–2091.

287. Joseph CA, Watson JM, Fern KJ. BCG immunisation in England and Wales: a survey of policy and practice in schoolchildren and neonates. *British Medical Journal* 1992;305(6852):495–498.

288. Colditz GA, Berkey CS, Mosteller F, Brewer TF *et al.* The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics* 1995;96(1:Pt 1):29–35.

289. Wasz-Hockert O, Genz H, Landmann H, Ocklitz HW. The effects of systematic BCG vaccination of newborn on the incidence of post-primary tuberculous meningitis in childhood. *Padiatrie und Grenzgebiete* 1989;28(6):365–370.

290. Altet Gomez MN, Alcaide MJ, Canela SJ, Serra ML, Salleras SL. Retrospective evaluation of the efficacy of the BCG vaccination campaign of newborns in Barcelona, Spain. *Tubercle & Lung Disease* 1993;74(2):100–105.

291. Criteria for discontinuation of vaccination programmes using Bacille Calmette-Guerin (BCG) in countries with a low prevalence of tuberculosis: a statement of the International Union Against Tuberculosis and Lung Disease. *Tubercle & Lung Disease* 1994;75(3):179–180.

292. Sutherland I. Effectiveness of BCG vaccination in England and Wales in 1983. *Tubercle* 1987;68(2): 81–92.

293. Sutherland I, Springett VH. The effects of the scheme for BCG vaccination of schoolchildren in England and Wales and the consequences of discontinuing the scheme at various dates. *Journal of Epidemiology & Community Health* 1989;43(1):15–24.

294. Ormerod LP, Charlett A, Gilham C, Darbyshire JH, Watson JM. Geographical distribution of tuberculosis notifications in national surveys of England and Wales in 1988 and 1993: report of the Public Health Laboratory Service/British Thoracic Society/Department of Health Collaborative Group. *Thorax* 1998;53(3):176–181.

295. Saeed M, Reid A, Nichols T, Rose AMC *et al. An update of the effect of a schools' BCG programme in England and Wales.* London: Health Protection Agency, 2002

296. Ormerod LP. Is new immigrant screening for tuberculosis still worthwhile? *Journal of Infection* 1998; 37(1):39–40.

297. Ormerod LP. Tuberculosis screening and prevention in new immigrants 1983–88. *Respiratory Medicine* 1990;84(4):269–271.

298. Colditz GA, Brewer TF, Berkey CS, Wilson ME *et al.* Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature. *Journal of the American Medical Association* 1994;271(9):698–702.

299. Chaloner JH, Ormerod LP. Assessment of the impact of BCG vaccination on tuberculosis incidence in south Asian adult immigrants. *Communicable Disease & Public Health* 2002;5(4):338–340.

300. Meredith S, Watson JM, Citron KM, Cockcroft A, Darbyshire JH. Are healthcare workers in England and Wales at increased risk of tuberculosis? *British Medical Journal* 1996;313(7056):522–525.

301. Brewer TF, Colditz GA. Bacille Calmette-Guerin vaccination for the prevention of tuberculosis in health care workers. *Clinical Infectious Diseases* 1995;20(1):136–142.

302. Jin BW, Hong YP, Kim SJ. A contact study to evaluate the BCG vaccination programme in Seoul. *Tubercle* 1989;70(4):241–248.

303. Capewell S, Leitch AG. The value of contact procedures for tuberculosis in Edinburgh. *British Journal of Diseases of the Chest* 1984;78(4):317–329.

304. Rubilar M, Brochwicz-Lewinski MJ, Anderson M, Leitch AG. The outcome of contact procedures for tuberculosis in Edinburgh, Scotland 1982–1991. *Respiratory Medicine* 1995;89(2):113–120.

305. Kritski AL, Marques MJ, Rabahi MF, Vieira MA *et al.* Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. *American Journal of Respiratory & Critical Care Medicine* 1996;153(1):331–335.

306. Esmonde TF, Petheram IS. Audit of tuberculosis contact tracing procedures in south Gwent. *Respiratory Medicine* 1991;85(5):421–424.

307. Hussain SF, Watura R, Cashman B, Campbell IA, Evans MR. Tuberculosis contact tracing: are the British Thoracic Society guidelines still appropriate? *Thorax* 1992;47(11):984–985.

308. Kumar S, Innes JA, Skinner C. Yield from tuberculosis contact tracing in Birmingham. *Thorax* 1992; 47:875.

309. Ormerod LP. Tuberculosis contact tracing. Blackburn 1982–90. *Respiratory Medicine* 1992;87(2):127–131.

310. Teale C, Cundall DB, Pearson SB. Time of development of tuberculosis in contacts. *Respiratory Medicine* 1991;85(6):475–477.

311. Ansari S, Thomas S, Campbell IA, Furness L, Evans MR. Refined tuberculosis contact tracing in a low incidence area. *Respiratory Medicine* 1998;92(9):1127–1131.

312. Hardinge FM, Black M, Chamberlain P. TB contact tracing in South Buckinghamshire from 1994 to mid 1998. *American Journal of Respiratory & Critical Care Medicine* 1999;159(Suppl): a303.

313. Irish C, Jolly E, Baker T. Contact tracing smear negative and non-pulmonary tuberculosis in a high incidence area. *Thorax* 1997;52(Suppl 6): a34.

314. Behr MA, Warren SA, Salamon H, Hopewell PC *et al.* Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet* 1999;353(9151):444–449.

315. Hernandez-Garduno E, Cook V, Kinimoto D, Elwood RK, Black WA. Transmission of tuberculosis from smear-negative patients: a molecular epidemiology study. *Thorax* 2004;59(4):286–290.

316. Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. *Bulletin of the International Union Against Tuberculosis* 1975;50(1):90–106.

317. Lobato MN, Royce SE, Mohle-Boetani JC. Yield of source-case and contact investigations in identifying previously undiagnosed childhood tuberculosis. *International Journal of Tuberculosis & Lung Disease* 2003;7(12 Suppl. 3):S391–S396.

318. Driver CR, Cordova IM, Munsiff SS. Targeting tuberculosis testing: the yield of source case investigations for young children with reactive tuberculin skin tests. *Public Health Reports* 2002;117(4):366–372.

319. Reichler MR, Reves R, Bur S, Thompson V *et al.* Evaluation of investigations conducted to detect and prevent transmission of tuberculosis. *Journal of the American Medical Association* 2002;287(8):991–995.

320. Liippo KK, Kulmala K, Tala EO. Focusing tuberculosis contact tracing by smear grading of index cases. *American Review of Respiratory Disease* 1993;148(1):235–236.

321. Hussain SF, Watura R, Cashman B, Campbell IA, Evans MR. Audit of a tuberculosis contact tracing clinic. *British Medical Journal* 1992;304(6836):1213–1215.

322. Del Castillo OD, Penafiel CM, Alvarez GF, Soto Campos JG, *et al.* Investigation of tuberculosis contacts in a nonhospital pneumology practice. *European Journal of Clinical Microbiology & Infectious Diseases* 1999;18(11):790–795.

323. Li J, Driver CR, Munsiff SS, Fujiwara PI. Finding contacts of homeless tuberculosis patients in New York City. *International Journal of Tuberculosis & Lung Disease* 2003;7(12 Suppl.3):S397–S404.

324. van Deutekom H, Hoijng SP, de Haas PE, Langendam MW *et al.* Clustered tuberculosis cases: do they represent recent transmission and can they be detected earlier? *American Journal of Respiratory & Critical Care Medicine* 2004;169(7):806–810.

325. Nitta AT, Knowles LS, Kim J, Lehnkering EL *et al.* Limited transmission of multidrug-resistant tuberculosis despite a high proportion of infectious cases in Los Angeles County, California. *American Journal of Respiratory & Critical Care Medicine* 2002;165(6):812–817.

326. Bishai WR, Graham NM, Harrington S, Pope DS *et al.* Molecular and geographic patterns of tuberculosis transmission after 15 years of directly observed therapy. *Journal of the American Medical Association* 1998;280(19):1679–1684.

327. Barnes PF, Yang Z, Preston-Martin S, Pogoda JM *et al.* Patterns of tuberculosis transmission in Central Los Angeles. *Journal of the American Medical Association* 1997;278(14):1159–1163.

328. Solsona J, Cayla JA, Verdu E, Estrada MP *et al.* Molecular and conventional epidemiology of tuberculosis in an inner city district. *International Journal of Tuberculosis & Lung Disease* 2001;5(8):724–731.

329. Ruddy MC, Davies AP, Yates MD, Yates S *et al.* Outbreak of isoniazid resistant tuberculosis in north London. *Thorax* 2004;59(4):279–285.

330. Veen J. Microepidemics of tuberculosis: the stone-in-the-pond principle. *Tubercle & Lung Disease* 1992;73(2):73–76.

331. PHLS. Enhanced surveillance of *Mycobacterium bovis* in humans. *Communicable Disease Weekly* 1998; 8(32):281–284.

332. Department of Health. *Bovine Tuberculosis guidance on management of the public health consequences of tuberculosis in cattle in England and Wales.* London: DH, 2000.

333. Lobue PA, LeClair JJ, Moser KS. Contact investigation for cases of pulmonary *Mycobacterium bovis*. *International Journal of Tuberculosis & Lung Disease* 2004;8(7):868–872.

334. Driver CR, Valway SE, Morgan WM, Onorato IM, Castro KG. Transmission of *Mycobacterium tuberculosis* associated with air travel. *Journal of the American Medical Association* 1994;272(13):1031–1035.

335. Whitlock G, Calder L, Perry H. A case of infectious tuberculosis on two long-haul aircraft flights: contact investigation. *New Zealand Medical Journal* 2001;114(1137):353–355.

336. Wang PD. Two-step tuberculin testing of passengers and crew on a commercial airplane. *American Journal of Infection Control* 2000;28(3):233–238.

337. Kenyon TA, Valway SE, Ihle WW, Onorato IM, Castro KG. Transmission of multi-drug-resistant *Mycobacterium tuberculosis* during a long airplane flight. *New England Journal of Medicine* 1996;334(15): 933–938.

338. Miller MA, Valway S, Onorato IM. Tuberculosis risk after exposure on airplanes. *Tubercle & Lung Disease* 1996;77(5):414–419.

339. Moore M, Fleming KS, Sands L. A passenger with pulmonary/laryngeal tuberculosis: no evidence of transmission on two short flights. *Aviation Space & Environmental Medicine* 1996;67(11):1097–1100.

340. Curtis AB, Ridzon R, Vogel R, McDonough S *et al.* Extensive transmission of *Mycobacterium tuberculosis* from a child. *New England Journal of Medicine* 1999;341(20):1491–1495.

341. Phillips L, Carlile J, Smith D. Epidemiology of a tuberculosis outbreak in a rural Missouri high school. *Pediatrics* 2004;113(6):e514–e519.

342. Ridzon R, Kent JH, Valway S, Weismuller P *et al.* Outbreak of drug-resistant tuberculosis with second-generation transmission in a high school in California. *Journal of Pediatrics* 1997;131(6):863–868.

343. The Lodi Tuberculosis Working Group. A school and community-based outbreak of *Mycobacterium tuberculosis* in northern Italy, 1992–3. *Epidemiology & Infection* 1994;113(1):83–93.

344. Rothman LM, Dubeski G. School contact tracing following a cluster of tuberculosis cases in two Scarborough schools. Canadian Journal of Public Health Revue 1993;84(5):297–302.

345. Sacks JJ, Brenner ER, Breeden DC, Anders HM, Parker RL. Epidemiology of a tuberculosis outbreak in a South Carolina junior high school. *American Journal of Public Health* 1985;75(4):361–365.

346. Calder L, Hampton L, Prentice D, Reeve M *et al.* A school and community outbreak of tuberculosis in Auckland. *New Zealand Medical Journal* 2000;113(1105):71–74.

347. Connolly K, Murphy C. A school outbreak of tuberculosis. *Irish Medical Journal* 1987;80(12):415.

348. Wales JM, Buchan AR, Cookson JB, Jones DA, Marshall BS. Tuberculosis in a primary school: the Uppingham outbreak. *British Medical Journal* (clinical research ed) 1985;291(6501):1039–1040.

349. Light IJ, Saidleman M, Sutherland JM. Management of newborns after nursery exposure to tuberculosis. *American Review of Respiratory Disease* 1974;109(4):415–419.

350. Agata E-MC, Wise S, Stewart A, Lefkowitz LB, Jr. Nosocomial transmission of *Mycobacterium tuberculosis* from an extrapulmonary site. *Infection Control & Hospital Epidemiology* 2001;22(1):10–12.

351. Drobniewski FA, Ferguson J, Barritt K, Higgins RM *et al.* Follow up of an immunocompromised contact group of a case of open pulmonary tuberculosis on a renal unit. *Thorax* 1995;50(8):863–868.

352. Zaza S, Blumberg HM, Beck-Sague C, Haas WH *et al.* Nosocomial transmission of *Mycobacterium tuberculosis*: role of health care workers in outbreak propagation. *Journal of Infectious Diseases* 1995; 172(6):1542–1549.

353. Zaza S, Beck-Sague CM, Jarvis WR. Tracing patients exposed to health care workers with tuberculosis. *Public Health Reports* 1997;112(2):153–157.

354. George RH, Gully PR, Gill ON, Innes JA *et al.* An outbreak of tuberculosis in a children's hospital. *Journal of Hospital Infection* 1986;8(2):129–142.

355. Medical Research Council Tuberculosis and Chest Diseases Unit. National survey of tuberculosis notifications in England and Wales 1978–9. *British Medical Journal* 1980;281(6245):895–898.

356. Bothamley GH, Rowan JP, Griffiths CJ, Beeks M *et al.* Screening for tuberculosis: the port of arrival scheme compared with screening in general practice and the homeless. *Thorax* 2002;57(1):45–49.

357. Verver S, Bwire R, Borgdorff MW. Screening for pulmonary tuberculosis among immigrants: estimated effect on severity of disease and duration of infectiousness. *International Journal of Tuberculosis & Lung Disease* 2001;5(5):419–425.

358. El Hamad I, Casalini C, Matteelli A, Casari S *et al.* Screening for tuberculosis and latent tuberculosis infection among undocumented immigrants at an unspecialised health service unit. *International Journal of Tuberculosis & Lung Disease* 2001;5(8):712–716.

359. Kelly PM, Scott L, Krause VL. Tuberculosis in East Timorese refugees: implications for health care needs in East Timor. *International Journal of Tuberculosis & Lung Disease* 2002;6(11):980–987.

360. Truong DH, Hedemark LL, Mickman JK, Mosher LB *et al.* Tuberculosis among Tibetan immigrants from India and Nepal in Minnesota, 1992-1995. *Journal of the American Medical Association* 1997;277(9): 735–738.

361. Nolan CM, Elarth AM. Tuberculosis in a cohort of South East Asian Refugees. A five-year surveillance study. *American Review of Respiratory Disease* 1988;137(4):805–809.

362. Capewell S, France AJ, Anderson M, Leitch AG. The diagnosis and management of tuberculosis in common hostel dwellers. *Tubercle* 1986;67(2):125–131.

363. Patel KR. Pulmonary tuberculosis in residents of lodging houses, night shelters and common hostels in Glasgow: a 5-year prospective survey. *British Journal of Diseases of the Chest* 1985;79(1):60–66.

364. Kumar D, Citron KM, Leese J, Watson JM. Tuberculosis among the homeless at a temporary shelter in London: report of a chest x ray screening programme. *Journal of Epidemiology & Community Health* 1995;49(6):629–633.

365. Griffin RG, Hoff GL. Tuberculosis screening in Kansas City homeless shelters. *Missouri Medicine* 1999;96(10):496–499.

366. Kermode M, Crofts N, Miller P, Speed B, Streeton J. Health indicators and risks among people experiencing homelessness in Melbourne, 1995–1996. *Australian & New Zealand Journal of Public Health* 1998;22(4):464–470.

367. Southern A, Premaratne N, English M, Balazs J, O'Sullivan D. Tuberculosis among homeless people in London: an effective model of screening and treatment. *International Journal of Tuberculosis & Lung Disease* 1999;3(11):1001–1008.

368. Layton MC, Cantwell MF, Dorsinville GJ, Valway SE *et al.* Tuberculosis screening among homeless persons with AIDS living in single-room-occupancy hotels. *American Journal of Public Health* 1995; 85(11):1556–1559.

369. Lunn JA, Mayho V. Incidence of pulmonary tuberculosis by occupation of hospital employees in the National Health Service in England and Wales 1980–84. *Journal of the Society of Occupational Medicine* 1989;39(1):30–32.

370. Hill A, Burge A, Skinner C. Tuberculosis in NHS hospital staff in the west Midlands region of England, 1992–5. *Thorax* 1997;52(11):994–997.

371. Wiggam SL, Hayward AC. Hospitals in England are failing to follow guidance for tuberculosis infection control – results of a National Survey. *Journal of Hospital Infection* 2000;46(4):257–262.

372. Bangsberg DR, Crowley K, Moss A, Dobkin JF *et al.* Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. *Infection Control & Hospital Epidemiology* 1997;18(8):566–570.

373. Blumberg HM, Watkins DL, Berschling JD, Antle A *et al.* Preventing the nosocomial transmission of tuberculosis. *Annals of Internal Medicine* 1995;122(9):658–663.

374. Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City. *American Journal of Infection Control* 1995;23(6):352–356.

375. Jereb JA, Klevens RM, Privett TD, Smith PJ *et al.* Tuberculosis in health care workers at a hospital with an outbreak of multidrug-resistant *Mycobacterium tuberculosis*. *Archives of Internal Medicine* 1995;155(8):854–859.

376. Behrman AJ, Shofer FS. Tuberculosis exposure and control in an urban emergency department. *Annals of Emergency Medicine* 1998;31(3):370–375.

377. Menzies D, Fanning A, Yuan L, FitzGerald JM. Hospital ventilation and risk for tuberculous infection in Canadian health care workers. Canadian Collaborative Group in Nosocomial Transmission of TB. *Annals of Internal Medicine* 2000;133(10):779–789.

378. Singh D, Sutton C, Woodcock A. Repeat tuberculin testing in BCG-vaccinated subjects in the United Kingdom. The booster effect varies with the time of reading. *American Journal of Respiratory & Critical Care Medicine* 2001;164(6):962–964.

379. Nursing and Midwifery Council. *The NMC Code of Professional Conduct: standards for conduct, performance and ethics.* London: NMC, 2004

380. Darbyshire JH. Tuberculosis in prisons. *British Medical Journal* 1989;299(6704):874.

381. Bock NN, Reeves M, LaMarre M, DeVoe B. Tuberculosis case detection in a state prison system. *Public Health Reports* 1998;113(4):359–364.

382. Saunders DL, Olive DM, Wallace SB, Lacy D *et al.* Tuberculosis screening in the federal prison system: an opportunity to treat and prevent tuberculosis in foreign-born populations. *Public Health Reports* 2001;116(3):210–218.

383. Klopf LC. Tuberculosis control in the New York State Department of Correctional Services: a case management approach. *American Journal of Infection Control* 1998;26(5):534–537.

384. Puisis M, Feinglass J, Lidow E, Mansour M. Radiographic screening for tuberculosis in a large urban county jail. *Public Health Reports* 1996;111(4):330–334.

385. Health and Safety Executive. *Respiratory protective equipment at work: a practical guide HSG53.* Sudbury: HSE Books, 2005. Available from **www.hsebooks.com/Books/**

386. Interdepartmental Working Group on Tuberculosis. *The prevention and control of tuberculosis in the United Kingdom: UK guidance on the prevention and control of transmission of 1. HIV-related tuberculosis 2. drug-resistant, including multiple drug-resistant, tuberculosis.* London: Department of Health, 1998.

16.1 References 2011

Anon Hospital Episode Statistics 2003: Provided data used in section 11 (Internet download)

Adetifa IM, Lugos MD, Hammond A et al. (2007) Comparison of two interferon gamma release assays in the diagnosis of Mycobacterium tuberculosis infection and disease in The Gambia. BMC Infectious Diseases 7: 122.

Alvarez-Leon EE, Espinosa-Vega E, Santana-Rodriguez E et al. (2009) Screening for tuberculosis infection in spanish healthcare workers: Comparison of the QuantiFERON-TB gold in-tube test with the tuberculin skin test. Infection Control & Hospital Epidemiology 30: 876-83.

Arend SM, Thijsen SF, Leyten EM et al. (2007) Comparison of two interferon-gamma assays and tuberculin skin test for tracing tuberculosis contacts.[see comment]. American Journal of Respiratory & Critical Care Medicine 175: 618-27.

Balcells ME, Perez CM, Chanqueo L et al. (2008) A comparative study of two different methods for the detection of latent tuberculosis in HIV-positive individuals in Chile. International Journal of Infectious Diseases 12: 645-52.

Bartalesi F, Vicidomini S, Goletti D et al. (2009) QuantiFERON-TB Gold and the TST are both useful for latent tuberculosis infection screening in autoimmune diseases. European Respiratory Journal 33: 586-93.

Brock I, Weldingh K, Lillebaek T et al. (2004) Comparison of tuberculin skin test and new specific blood test in tuberculosis contacts.[see comment]. American Journal of Respiratory & Critical Care Medicine 170: 65-9.

Brodie D, Lederer DJ, Gallardo JS et al. (2008) Use of an interferon-gamma release assay to diagnose latent tuberculosis infection in foreign-born patients. Chest 133: 869-74.

Casas I, Latorre I, Esteve M et al. (2009) Evaluation of interferon-gamma release assays in the diagnosis of recent tuberculosis infection in health care workers. PLoS ONE [Electronic Resource] 4: e6686.

Chun JK, Kim CK, Kim HS et al. (2008) The role of a whole blood interferon-gamma assay for the detection of latent tuberculosis infection in Bacille Calmette-Guerin vaccinated children. Diagnostic Microbiology & Infectious Disease 62: 389-94.

Cobanoglu N, Ozcelik U, Kalyoncu U et al. (2007) Interferon-gamma assays for the diagnosis of tuberculosis infection before using tumour necrosis factor-alpha blockers. International Journal of Tuberculosis & Lung Disease 11: 1177-82.

Connell TG, Curtis N, Ranganathan SC et al. (2006) Performance of a whole blood interferon gamma assay for detecting latent infection with Mycobacterium tuberculosis in children.[see comment]. Thorax 61: 616-20.

Cummings KJ, Smith TS, Shogren ES et al. (2009) Prospective comparison of tuberculin skin test and QuantiFERON-TB Gold In-Tube assay for the detection of latent tuberculosis infection among healthcare workers in a low-incidence setting. Infection Control & Hospital Epidemiology 30: 1123-6.

Diel R, Loddenkemper R, Meywald-Walter K et al. (2009) Comparative performance of tuberculin skin test, QuantiFERON-TB-Gold In Tube assay, and T-Spot.TB test in contact investigations for tuberculosis. Chest 135: 1010-8.

Diel R, Loddenkemper R, Meywald-Walter K et al. (2008) Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with Mycobacterium tuberculosis.[see comment]. American Journal of Respiratory & Critical Care Medicine 177: 1164-70.

Girardi E, Angeletti C, Puro V et al. Estimating diagnostic accuracy of tests for latent tuberculosis infection without a gold standard among healthcare workers.[see comment]. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin 14: 2009.

Hansted E, Andriuskeviciene A, Sakalauskas R et al. (2009) T-cell-based diagnosis of tuberculosis infection in children in Lithuania: a country of high incidence despite a high coverage with bacille Calmette-Guerin vaccination. BMC Pulmonary Medicine 9: 41.

Harada N, Nakajima Y, Higuchi K et al. (2006) Screening for tuberculosis infection using whole-blood interferon-gamma and Mantoux testing among Japanese healthcare workers. Infection Control & Hospital Epidemiology 27: 442-8.

Hesseling AC, Mandalakas AM, Kirchner HL et al. (2009) Highly discordant T cell responses in individuals with recent exposure to household tuberculosis. Thorax 64: 840-6.

Higuchi K, Harada N, Mori T et al. (2007) Use of QuantiFERON-TB Gold to investigate tuberculosis contacts in a high school. Respirology 12: 88-92.

Higuchi K, Kondo S, Wada M et al. (2009) Contact investigation in a primary school using a whole blood interferon-gamma assay. Journal of Infection 58: 352-7.

Hotta K, Ogura T, Nishii K et al. (2007) Whole blood interferon-gamma assay for baseline tuberculosis screening among Japanese healthcare students. PLoS ONE 2

Janssens JP, Roux-Lombard P, Perneger T et al. (2008) Contribution of a IFN-gamma assay in contact tracing for tuberculosis in a low-incidence, high immigration area. Swiss Medical Weekly 138: 585-93.

Jones S, de GD, Wallach FR et al. (2007) Utility of QuantiFERON-TB Gold in-tube testing for latent TB infection in HIV-infected individuals. International Journal of Tuberculosis & Lung Disease 11: 1190-5.

Kang YA, Lee HW, Yoon HI et al. (2005) Discrepancy between the tuberculin skin test and the whole-blood interferon gamma assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country.[see comment]. JAMA 293: 2756-61.

Kik SV, Franken WP, Arend SM et al. (2009) Interferon-gamma release assays in immigrant contacts and effect of remote exposure to Mycobacterium tuberculosis. International Journal of Tuberculosis & Lung Disease 13: 820-8.

Lighter J, Rigaud M, Eduardo R et al. (2009) Latent tuberculosis diagnosis in children by using the QuantiFERON-TB Gold In-Tube test. Pediatrics 123: 30-7.

Luetkemeyer AF, Charlebois ED, Flores LL et al. (2007) Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. American Journal of Respiratory & Critical Care Medicine 175: 737-42.

Mandalakas AM, Hesseling AC, Chegou NN et al. (2008) High level of discordant IGRA results in HIV-infected adults and children. International Journal of Tuberculosis & Lung Disease 12: 417-23.

Manuel O, Humar A, Preiksaitis J et al. (2007) Comparison of quantiferon-TB gold with tuberculin skin test for detecting latent tuberculosis infection prior to liver transplantation. American Journal of Transplantation 7: 2797-801.

Matulis G, Juni P, Villiger PM et al. (2008) Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a Mycobacterium tuberculosis antigen-specific interferon gamma assay. Annals of the Rheumatic Diseases 67: 84-90.

Mirtskhulava V, Kempker R, Shields KL et al. (2008) Prevalence and risk factors for latent tuberculosis infection among health care workers in Georgia. International Journal of Tuberculosis & Lung Disease 12: 513-9.

National Institute for Health and Clinical Excellence (2005) Guideline development methods: information for national collaborating centres and guideline developers

O'Neal S, Hedberg K, Markum A et al. (2009) Discordant tuberculin skin and interferon-gamma tests during contact investigations: a dilemma for tuberculosis controllers. International Journal of Tuberculosis & Lung Disease 13: 662-4.

Okada K, Mao TE, Mori T et al. (2008) Performance of an interferon-gamma release assay for diagnosing latent tuberculosis infection in children. Epidemiology & Infection 136: 1179-87.

Pai M, Gokhale K, Joshi R et al. (2005) Mycobacterium tuberculosis infection in health care workers in rural India: comparison of a whole-blood interferon gamma assay with tuberculin skin testing.[see comment]. JAMA 293: 2746-55.

Piana F, Codecasa LR, Cavallerio P et al. (2006) Use of a T-cell-based test for detection of tuberculosis infection among immunocompromised patients. European Respiratory Journal 28: 31-4.

Ponce de LD, Acevedo-Vasquez E, Alvizuri S et al. (2008) Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. Journal of Rheumatology 35: 776-81.

Porsa E, Cheng L, Graviss EA (2007) Comparison of an ESAT-6/CFP-10 peptide-based enzyme-linked immunospot assay to a tuberculin skin test for screening of a population at moderate risk of contracting tuberculosis. Clinical & Vaccine Immunology: CVI 14: 714-9.

Porsa E, Cheng L, Seale MM et al. (2006) Comparison of a new ESAT-6/CFP-10 peptide-based gamma interferon assay and a tuberculin skin test for tuberculosis screening in a moderate-risk population. Clinical & Vaccine Immunology: CVI 13: 53-8.

Richeldi L, Losi M, D'Amico R et al. (2009) Performance of tests for latent tuberculosis in different groups of immunocompromised patients. Chest 136: 198-204.

Schoepfer AM, Flogerzi B, Fallegger S et al. (2008) Comparison of interferon-gamma release assay versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease. American Journal of Gastroenterology 103: 2799-806.

Shovman O, Anouk M, Vinnitsky N et al. (2009) QuantiFERON-TB Gold in the identification of latent tuberculosis infection in rheumatoid arthritis: a pilot study. International Journal of Tuberculosis & Lung Disease 13: 1427-32.

Soborg B, Ruhwald M, Hetland ML et al. (2009) Comparison of screening procedures for Mycobacterium tuberculosis infection among patients with inflammatory diseases. Journal of Rheumatology 36: 1876-84.

Talati NJ, Seybold U, Humphrey B et al. (2009) Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. BMC Infectious Diseases 9: 15.

Topic RZ, Dodig S, Zoricic-Letoja I (2009) Interferon-gamma and immunoglobulins in latent tuberculosis infection. Archives of Medical Research 40: 103-8.

Tripodi D, Brunet-Court, Nael V et al. (2009) Evaluation of the tuberculin skin test and the interferon-gamma release assay for TB screening in French healthcare workers. Journal of Occupational Medicine & Toxicology 4: 30.

Vassilopoulos D, Stamoulis N, Hadziyannis E et al. (2008) Usefulness of enzyme-linked immunospot assay (Elispot) compared to tuberculin skin testing for latent tuberculosis screening in rheumatic patients scheduled for anti-tumor necrosis factor treatment.[see comment]. Journal of Rheumatology 35: 1271-6.

Vinton P, Mihrshahi S, Johnson P et al. (2009) Comparison of QuantiFERON-TB Gold In-Tube Test and tuberculin skin test for identification of latent Mycobacterium tuberculosis infection in healthcare staff and association between positive test results and known risk factors for infection. Infection Control & Hospital Epidemiology 30: 215-21.

Winje BA, Oftung F, Korsvold GE et al. (2008) Screening for tuberculosis infection among newly arrived asylum seekers: comparison of QuantiFERONTB Gold with tuberculin skin test. BMC Infectious Diseases 8: 65.

Zellweger JP, Zellweger A, Ansermet S et al. (2005) Contact tracing using a new T-cell-based test: better correlation with tuberculosis exposure than the tuberculin skin test. International Journal of Tuberculosis & Lung Disease 9: 1242-7.

Zhao X, Mazlagic D, Flynn EA et al. (2009) Is the QuantiFERON-TB blood assay a good replacement for the tuberculin skin test in tuberculosis screening? a pilot study at Berkshire Medical Center. American Journal of Clinical Pathology 132: 678-86.